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[54] **MEDICAL DEVICES WITH LONG TERM NON-THROMBOGENIC COATINGS**

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[73] Assignee: **Schneider (USA) Inc.**, Minneapolis, Minn.

[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] Appl. No.: **08/663,518**

[22] Filed: **Jun. 13, 1996**

Related U.S. Application Data

[63] Continuation-in-part of application No. 08/526,273, Sep. 11, 1995, abandoned, and a continuation-in-part of application No. 08/424,884, Apr. 19, 1995, abandoned.

[51] **Int. Cl.**[7] **A61F 2/06**

[52] **U.S. Cl.** **623/1.43**; 623/1.18; 623/1.46; 424/424; 427/2.21; 427/2.24

[58] **Field of Search** 623/1, 11, 12, 623/1.15, 1.18, 1.42, 1.43, 1.44, 1.45, 1.46; 606/191, 194, 195; 604/890.1, 891.1; 424/422, 423, 424; 427/2.1, 2.12, 2.24, 2.21

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[57] **ABSTRACT**

A coating and method for implantable open lattice metallic stent prostheses are disclosed. The coating includes a relatively thin layer of biostable elastomeric material containing an amount of biologically active material, particularly heparin, dispersed in the coating in combination with a non-thrombogenic surface. In one embodiment, the surface is provided with sites of high electronegativity species by coating with fluorosilicone which aid in controlling elution, particularly the initial release rate, and reduced thrombogenic activity. Other non-thrombogenic outer layers for heparin such as covalently bound polyethylene glycol (PEG) are also disclosed.

12 Claims, 8 Drawing Sheets

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Figure 1

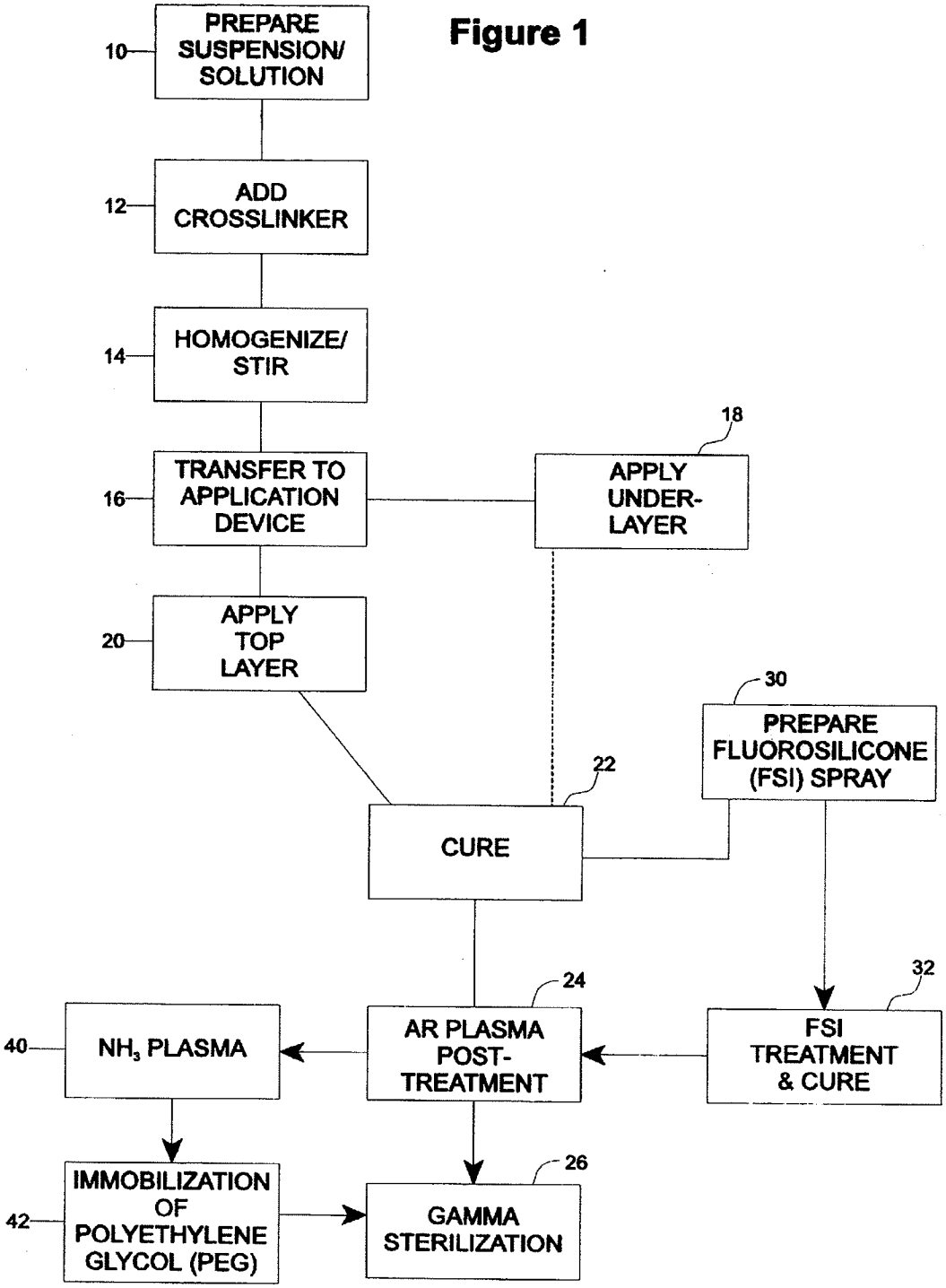
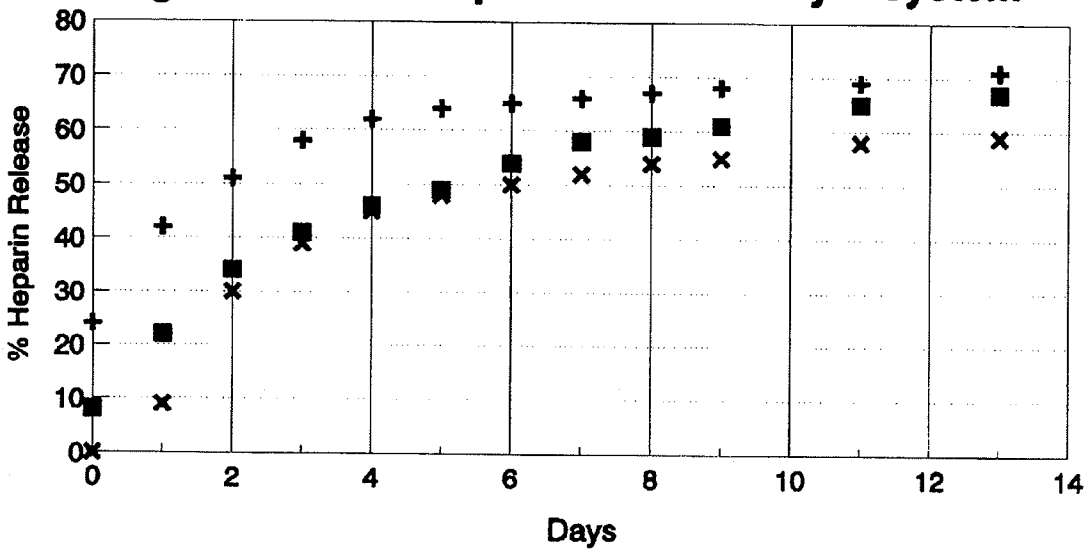

10
PREPARE SUSPENSION/ SOLUTION
12
ADD CROSSLINKER
14
HOMOGENIZE/ STIR
16
TRANSFER TO APPLICATION DEVICE
18
APPLY UNDER-LAYER
20
APPLY TOP LAYER
30
PREPARE FLUOROSILICONE (FSI) SPRAY
22
CURE
24
AR PLASMA POST-TREATMENT
32
FSI TREATMENT & CURE
40
NH3 PLASMA
42
IMMOBILIZATION OF POLYETHYLENE GLYCOL (PEG)
26
GAMMA STERILIZATION

Figure 2. Release profile for multilayer system

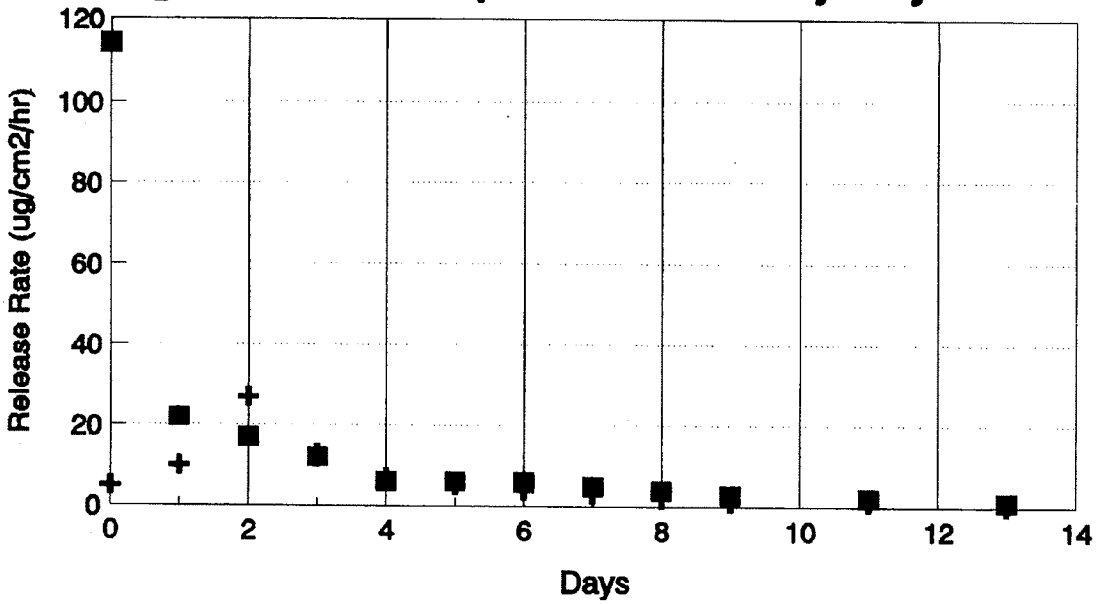


× Tie Layer = 37.5% Hep coating, top layer = silicone

■ Tie Layer = 37.5% Hep coating, top layer = 16.7% Hep coating

\+ Single Layer = 37.5% Hep coating

Figure 3. Release profile for multilayer system



+ Tie Layer = 37.5% Hep coating, top layer = silicone

▪ Tie Layer = 37.5% Hep coating, top layer = 16.7% Hep coating

Figure 4. Release kinetics for different drug loading at the similar coating thickness

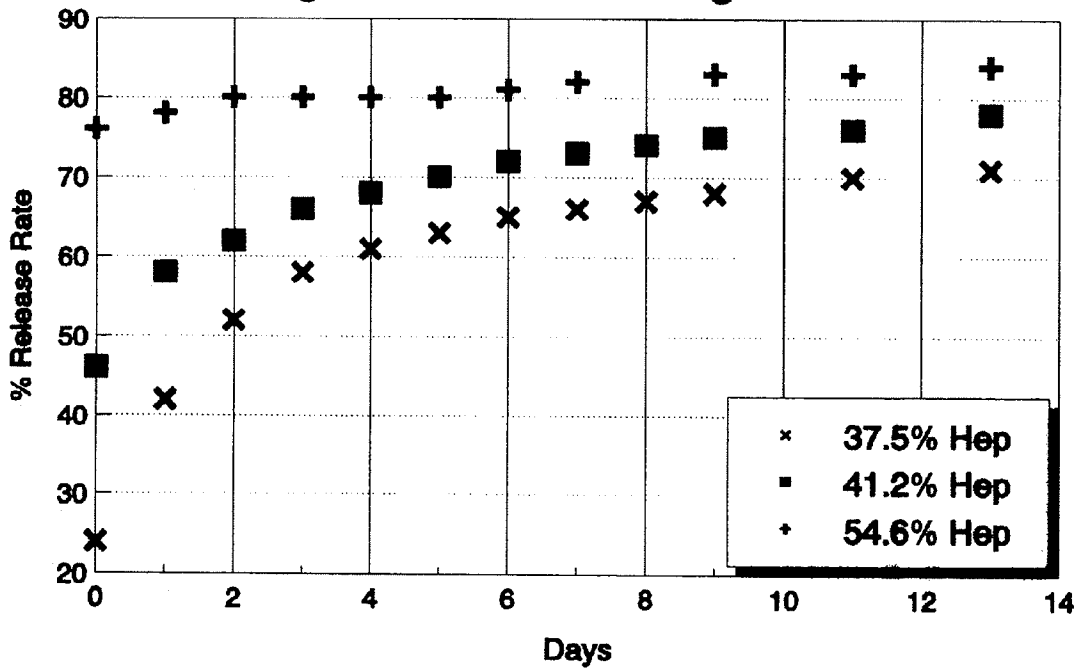


Figure 5. Drug elution kinetics at different coating thickness (A ~ 10-15um). Drug loading = 41.1%

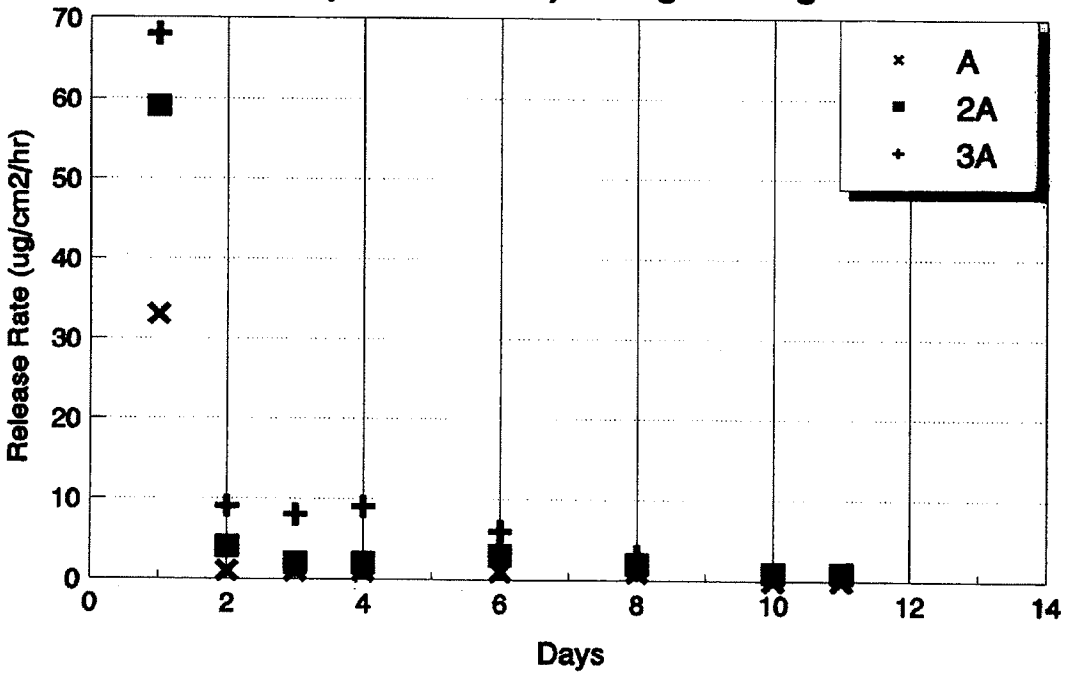


Figure 6. 37.5% Hep in tie-coat with the same tie-coat thickness and 16.7% Hep in top-coat

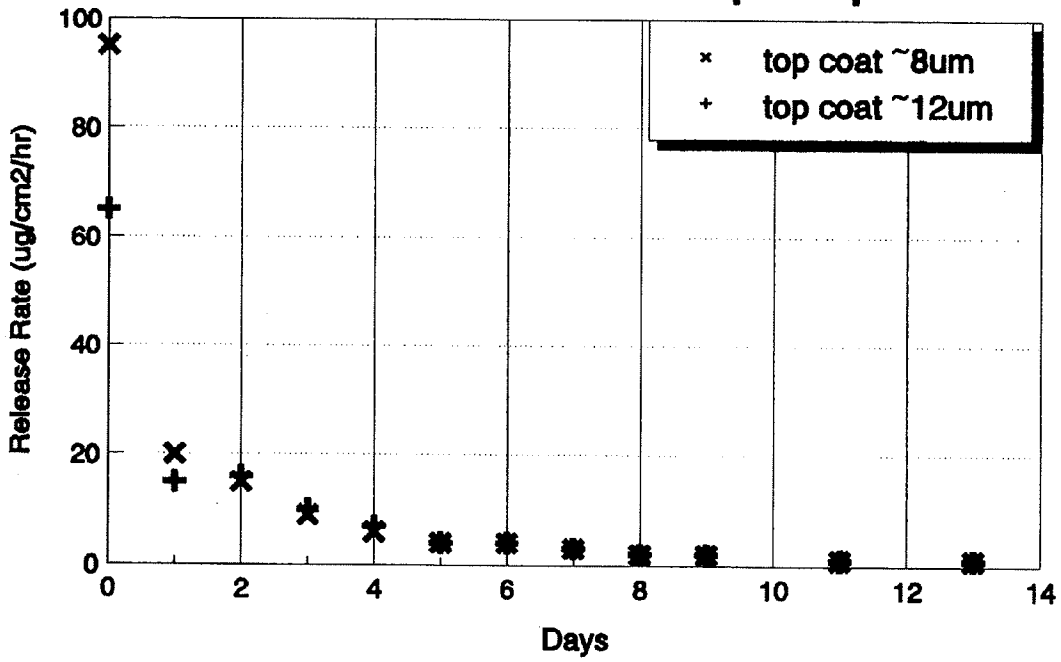


Figure 7. W or w/o fluorosilicone (FSI) top coat

Note: release rate for the coating w/o FSI is 25 times higher than w/FSI at the first two hrs (not plotted)

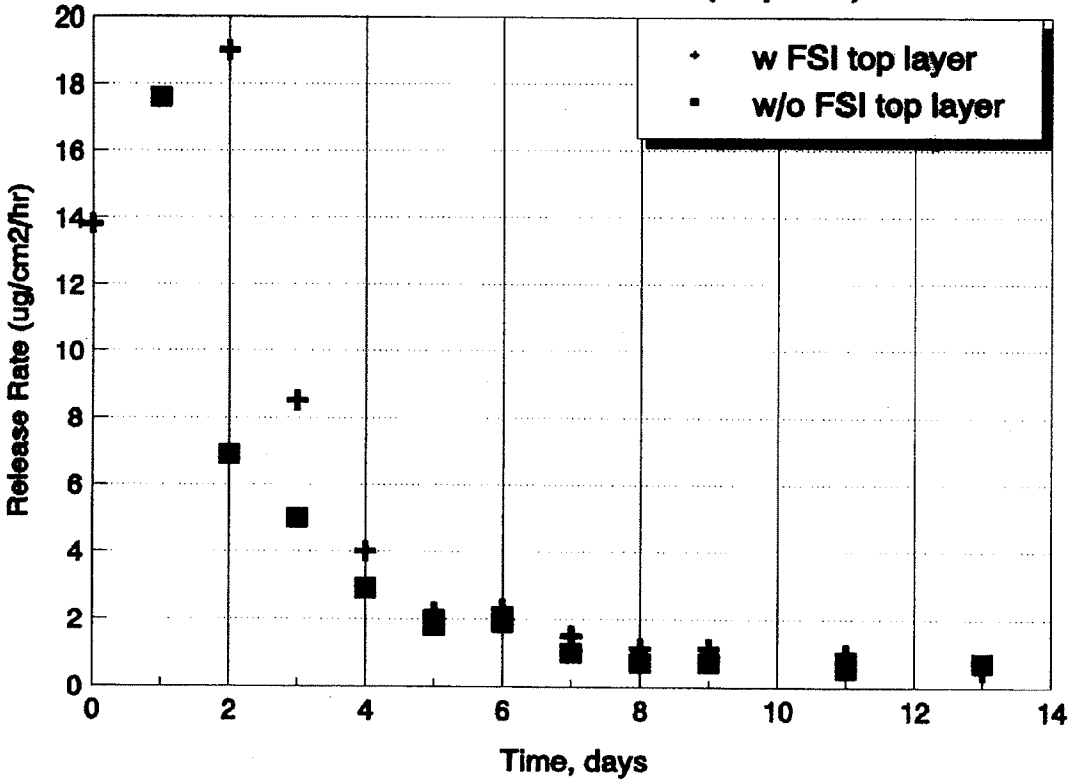
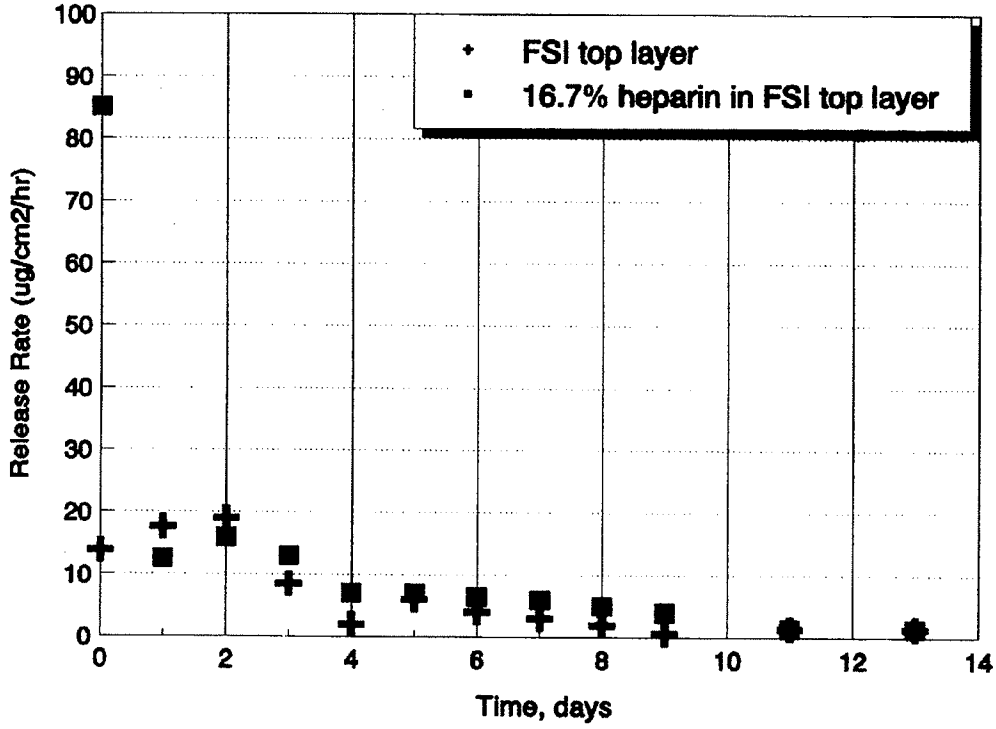


Figure 8. Comparison of fluorosilicone (FSI) top coat w or w/o heparin. The thickness of the tie coat (37.5%) heparin is about 40 micron.



MEDICAL DEVICES WITH LONG TERM NON-THROMBOGENIC COATINGS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a Continuation-In-Part of application Ser. No. 08/526,273, filed Sep. 11, 1995, now abandoned, and a Continuation-In-Part of application Ser. No. 08/424,884, filed Apr. 19, 1995, now abandoned, all portions of the parent applications not contained in this application being deemed incorporated by reference for any purpose. Cross-reference is also made to Ser. No. 08/663,490, entitled "DRUG RELEASE STENT COATING PROCESS, filed of even date, of common inventorship and assignee, now U.S. Pat. No. 5,837,313 and also a Continuation-In-Part of both above-referenced applications. To the extent that it is not contained herein, that application is also deemed incorporated herein by reference for any purpose.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to providing biostable elastomeric coatings on the surfaces of implants which incorporate biologically active species having controlled release characteristics in the coating particularly to providing a non-thrombogenic surface during and after timed release of the biologically active species. The invention is particularly described in terms of coatings on therapeutic expandable stent prostheses for implantation in body lumens, e.g., vascular implantation.

2. Related Art

In surgical or other related invasive procedures, the insertion and expansion of stent devices in blood vessels, urinary tracts or other locations difficult to otherwise access for the purpose of preventing restenosis, providing vessel or lumen wall support or reinforcement and for other therapeutic or restorative functions has become a common form of long-term treatment. Typically, such prostheses are applied to a location of interest utilizing a vascular catheter, or similar transluminal device, to carry the stent to the location of interest where it is thereafter released to expand or be expanded in situ. These devices are generally designed as permanent implants which may become incorporated in the vascular or other tissue which they contact at implantation.

One type of self-expanding stent has a flexible tubular body formed of several individual flexible thread elements each of which extends in a helix configuration with the centerline of the body serving as a common axis. The elements are wound in the same direction but are displaced axially relative to each other and meet, under crossing, a like number of elements also so axially displaced, but having the opposite direction of winding. This configuration provides a resilient braided tubular structure which assumes stable dimensions upon relaxation. Axial tension produces elongation and corresponding diameter contraction that allows the stent to be mounted on a catheter device and conveyed through the vascular system as a narrow elongated device. Once tension is relaxed in situ, the device at least substantially reverts to its original shape. Prostheses of the class including a braided flexible tubular body are illustrated and described in U.S. Pat. Nos. 4,655,771 and 4,954,126 to Wallsten and U.S. Pat. No. 5,061,275 to Wallsten et al.

Implanted stents have been used to carry medicinal agents, such as thrombolytic agents. U.S. Pat. No. 5,163,952 to Froix discloses a thermal memoried expanding plastic stent device formulated to carry a medicinal agent in the material of the stent itself. Pinchuk, in U.S. Pat. No. 5,092,877, discloses a stent of a polymeric material which may have a coating associated with the delivery of drugs. Other patents which are directed to devices of the class utilizing bio-degradable or bio-sorbable polymers include Tang et al, U.S. Pat. No. 4,916,193, and MacGregor, U.S. Pat. No. 4,994,071.

A patent to Sahatjian, U.S. Pat. No. 5,304,121, discloses a coating applied to a stent consisting of a hydrogel polymer and a preselected drug such as cell growth inhibitors or heparin. A further method of making a coated intravascular stent carrying a therapeutic material is described in Berg et al., U.S. Pat. No. 5,464,650, issued on Nov. 7, 1995 and corresponding to European Patent Application No. 0 623 354 A1 published Nov. 9, 1994. In that disclosure, a polymer coating material is dissolved in a solvent and the therapeutic material dispersed in the solvent; the solvent evaporated after application.

An article by Michael N. Helmus (a co-inventor of the present invention) entitled "Medical Device Design—A Systems Approach: Central Venous Catheters", 22nd International Society for the Advancement of Material and Process Engineering Technical Conference (1990) relates to polymer/drug/membrane systems for releasing heparin. Those polymer/drug/membrane systems require two distinct types of layers to function.

It has been recognized that contacting blood with the surface of a foreign body in vivo has a tendency to induce thrombogenic responses and that as the surface area of a foreign device in contact with host blood increases, the tendency for coagulation and clot forming at these surfaces also increases. This has led to the use of immobilized systemic anti-coagulant or thrombolytic agents such as heparin on blood contacting surfaces such as oxygen uptake devices to reduce this phenomenon. Such an approach is described by Winters, et al., in U.S. Pat. Nos. 5,182,317; 5,262,451 and 5,338,770 in which the amine functional groups of the active material are covalently bonded using polyethylene oxide (PEO) on a siloxane surface.

Another approach is described in U.S. Pat. No. 4,613,665 to Larm in which heparin is chemically covalently bound to plastic surface materials containing primary amino groups to impart a non-thrombogenic surface to the material. Other approaches for bonding heparin are described in Barbucci, et al., "Coating of commercially available materials with a new heparinizable material", *Journal of Biomedical Materials Research*, Vol 25, 1259–1274 (1991); Hubbell, J. A., "Pharmacologic Modification of Materials", *Cardiovascular Pathology*, Vol 2, No 3(Suppl.), 121S–127S (1993); Gravlee, G. P., "Heparin-Coated Cardiopulmonary Bypass Circuits", *Journal of Cardiothoracic and Vascular Anesthesia*, Vol 8, No 2, pp 213–222 (1994).

Although polymeric stents are effective, they, may have mechanical properties that are inferior to those of metal stents of like thickness and weave. Metallic vascular stents braided of even relatively fine metal can provide a large amount of strength to resist inwardly directed circumferential pressure. A polymer material of comparable strength requires a much thicker-walled structure or heavier, denser filament weave, which in turn, reduces the cross-sectional area available for flow through the stent and/or reduces the relative amount of open space in the weave. Also, it is usually more difficult to load and deliver polymeric stents using catheter delivery systems.

While certain types of stents such as braided metal stents may be preferred for some applications, the coating and coating modification process of the present invention is not so limited and can be used on a wide variety of prosthetic devices. Thus, in the case of stents, the present invention also applies, for example, to the class of stents that are not self-expanding including those which can be expanded, for instance, with a balloon; and is applicable to polymeric stents of all kinds. Other medical devices that can benefit from the present invention include blood exchanging devices, vascular access ports, central venus catheters, cardiovascular catheters, extracorpeal circuits, vascular grafts, pumps, heart valves, and cardiovascular sutures, to name a few. Regardless of detailed embodiments, applicability of the invention should not be considered limited with respect to implant design, implant location or materials of construction. Further, the present invention may be used with other types of implantable prostheses.

Accordingly, it is a primary object of the present invention to provide a coating and process for coating a stent to be used as a deployed stent prostheses, the coating being capable of effective controlled long-term delivery of biologically active materials.

Another object of the invention is to provide a coating and process for coating a stent prostheses using a biostable hydrophobic elastomer in which biologically active species are incorporated within a coating.

Still another object of the present invention is to provide a multi-layer coating and process for the delivery of biologically active species in which the percentage of active material can vary from layer to layer.

Yet another object of the present invention is to provide a multi-layer coating and process for the delivery of biologically active species from a coating with a non-thrombogenic surface.

A further object of the invention is to provide a multi-layer coating for the delivery of biologically active species such as heparin having a fluorosilicone top layer.

A still further object of the invention is to provide a multi-layer coating for the delivery of biologically active species such as heparin having a surface containing immobilized polyethylene glycol (PEG).

Other objects and advantages of the present invention will become apparent to those skilled in the art upon familiarization with the specification and appended claims.

SUMMARY OF THE INVENTION

The present invention provides a relatively thin layered coating of biostable elastomeric material containing an amount of biologically active material dispersed therein in combination with a non-thrombogenic surface that is useful for coating the surfaces of prostheses such as deployable stents.

The preferred stent to be coated is a self-expanding, open-ended tubular stent prostheses. Although other materials, including polymer materials, can be used, in the preferred embodiment, the tubular body is formed of a self-expanding open braid of fine single or polyfilament metal wire which flexes without collapsing, readily axially deforms to an elongate shape for transluminal insertion via a vascular catheter and resiliently expands toward predetermined stable dimensions upon removal in situ.

In the process, the initial coating is preferably applied as a mixture, solution or suspension of polymeric material and finely divided biologically active species dispersed in an organic vehicle or a solution or partial solution of such species in a solvent or vehicle for the polymer and/or biologically active species. For the purpose of this application, the term "finely divided" means any type or size of included material from dissolved molecules through suspensions, colloids and particulate mixtures. The active material is dispersed in a carrier material which may be the polymer, a solvent, or both. The coating is preferably applied as a plurality of relatively thin layers sequentially applied in relatively rapid sequence and is preferably applied with the stent in a radially expanded state.

In many applications the layered coating is referred to or characterized as including an undercoat and topcoat. The coating thickness ratio of the topcoat to undercoat may vary with the desired effect and/or the elution system. Typically these are of different formulations with most or all of the active material being contained in the undercoat and a non-thrombogenic surface is found in the topcoat.

The coating may be applied by dipping or spraying using evaporative solvent materials of relatively high vapor pressure to produce the desired viscosity and quickly establish coating layer thicknesses. The preferred process is predicated on reciprocally spray coating a rotating radially expanded stent employing an air brush device. The coating process enables the material to adherently conform to and cover the entire surface of the filaments of the open structure of the stent but in a manner such that the open lattice nature of the structure of the braid or other pattern is preserved in the coated device.

The coating is exposed to room temperature ventilation for a predetermined time (possibly one hour or more) for solvent vehicle evaporation. In the case of certain undercoat materials, thereafter the polymer material is cured at room temperature or elevated temperatures. Curing is defined as the process of converting the elastomeric or polymeric material into the finished or useful state by the application of heat and/or chemical agents which induce physico-chemical changes. Where, for example, polyurethane thermoplastic elastomers are used as an undercoat material, solvent evaporation can occur at room temperature rendering the undercoat useful for controlled drug release without further curing.

The applicable ventilation time and temperature for cure are determined by the particular polymer involved and particular drugs used. For example, silicone or polysiloxane materials (such as polydimethylsiloxane) have been used successfully. Urethane pre-polymers can also be utilized. Unlike the polyurethane thermoplastic elastomers, some of these materials are applied as pre-polymers in the coating composition and must thereafter be heat cured. The preferred silicone species have relatively low cure temperatures and are known as a room temperature vulcanizable (RTV) materials. Some polydimethylsiloxane materials can be cured, for example, by exposure to air at about 90° C. for a period of time such as 16 hours. A curing step may be implemented both after application of the undercoat or a certain number of lower layers and the top layers or a single curing step used after coating is completed.

The coated stents may thereafter be subjected to a post-cure process which includes an inert gas plasma treatment, and sterilization which may include gamma radiation, ETO treatment, electron beam or steam treatment.

In the plasma treatment, unconstrained coated stents are placed in a reactor chamber and the system is purged with nitrogen and a vacuum applied to 20–50 mTorr. Thereafter, inert gas (argon, helium or mixture of them) is admitted to

the reaction chamber for the plasma treatment. One method uses argon (Ar) gas, operating at a power range from 200 to 400 watts, a flow rate of 150–650 standard ml per minute, which is equivalent to about 100–450 mTorr, and an exposure time from 30 seconds to about 5 minutes. The stents can be removed immediately after the plasma treatment or remain in the argon atmosphere for an additional period of time, typically five minutes.

In accordance with the invention, the top coat or surface coating may be applied in any of several ways to further control thrombolitic effects and optionally, control the release profile especially the initial very high release rate associated with the elution of heparin.

In one embodiment, an outer layer of fluorosilicone (FSi) is applied to the undercoat as a topcoat. The outer layer can also contain heparin. In another embodiment, polyethylene glycol (PEG) is immobilized on the surface of the coating. In this process, the underlayer is subjected to inert gas plasma treatment and immediately thereafter is treated by ammonia (NH_3) plasma to aminate the surface. Amination, as used in this application, means creating mostly imino groups and other nitro containing species on the surface. This is followed by immediate immersion into electrophillically activated polyethylene glycol(PEG) solution with a reductive agent, i.e., sodium cyanoborohydride.

The coated and cured stents having the modified outer layer or surface are subjected to a final gamma radiation sterilization nominally at 2.5–3.5 Mrad. Argon (Ar) plasma treated stents enjoy full resiliency after radiation whether exposed in a constrained or non-constrained status, while constrained stents subjected to gamma sterilization without Ar plasma pretreatment lose resiliency and do not recover at a sufficient or appropriate rate.

The elastomeric materials that form the stent coating underlayers should possess certain properties. Preferably the layers should be of suitable hydrophobic biostable elastomeric materials which do not degrade. Surface layer material should minimize tissue rejection and tissue inflammation and permit encapsulation by tissue adjacent the stent implantation site. Exposed material is designed to reduce clotting tendencies in blood contacted and the surface is preferably modified accordingly. Thus, underlayers of the above materials are preferably provided with a fluorosilicone outer coating layer which may or may not contain imbedded bioactive material, such as heparin. Alternatively, the outer coating may consist essentially of polyethylene glycol (PEG), polysaccharides, phospholipids, or combinations of the foregoing.

Polymers generally suitable for the undercoats or underlayers include silicones (e.g., polysiloxanes and substituted polysiloxanes), polyurethanes, thermoplastic elastomers in general, ethylene vinyl acetate copolymers, polyolefin elastomers, polyamide elastomers, and EPDM rubbers. The above-referenced materials are considered hydrophobic with respect to the contemplated environment of the invention. Surface layer materials include fluorosilicones and polyethylene glycol (PEG), polysaccharides, phospholipids, and combinations of the foregoing.

While heparin is preferred as the incorporated active material, agents possibly suitable for incorporation include antithrobotics, anticoagulants, antibiotics, antiplatelet agents, thorombolytics, antiproliferatives, steroidal and non-steroidal antinflammatories, agents that inhibit hyperplasia and in particular restenosis, smooth muscle cell inhibitors, growth factors, growth factor inhibitors, cell adhesion inhibitors, cell adhesion promoters and drugs that may enhance the formation of healthy neointimal tissue, including endothelial cell regeneration. The positive action may come from inhibiting particular cells (e.g., smooth muscle cells) or tissue formation (e.g., fibromuscular tissue) while encouraging different cell migration (e.g., endothelium) and tissue formation (neointimal tissue).

Suitable materials for fabricating the braided stent include stainless steel, tantalum, titanium alloys including nitinol (a nickel titanium, thermomemoried alloy material), and certain cobalt alloys including cobalt-chromium-nickel alloys such as Elgiloy® and Phynox®. Further details concerning the fabrication and details of other aspects of the stents themselves may be gleaned from the above referenced U.S. Pat. Nos. 4,655,771 and 4,954,126 to Wallsten and U.S. Pat. No. 5,061,275 to Wallsten et al, which are incorporated by reference herein.

Various combinations of polymer coating materials can be coordinated with biologically active species of interest to produce desired effects when coated on stents to be implanted in accordance with the invention. Loadings of therapeutic materials may vary. The mechanism of incorporation of the biologically active species into the surface coating and egress mechanism depend both on the nature of the surface coating polymer and the material to be incorporated. The mechanism of release also depends on the mode of incorporation. The material may elute via interparticle paths or be administered via transport or diffusion through the encapsulating material itself.

For the purposes of this specification, "elution" is defined as any process of release that involves extraction or release by direct contact of the material with bodily fluids through the interparticle paths connected with the exterior of the coating. "Transport" or "diffusion" are defined to include a mechanism of release in which the material released traverses through another material.

The desired release rate profile can be tailored by varying the coating thickness, the radial distribution (layer to layer) of bioactive materials, the mixing method, the amount of bioactive material, the combination of different matrix polymer materials at different layers, and the crosslink density of the polymeric material. The crosslink density is related to the amount of crosslinking which takes place and also the relative tightness of the matrix created by the particular crosslinking agent used. This, during the curing process, determines the amount of crosslinking and also the crosslink density of the polymer material. For bioactive materials released from the crosslinked matrix, such as heparin, a denser crosslink structure will result in a longer release time and reduced burst effect.

It will also be appreciated that an unmedicated silicone thin top layer provides some advantage and additional control over drug elusion; however, in the case of heparin, for example, it has been found that a top coat or surface coating modified to further control the initial heparin release profile or to make the surface more non-thrombogenic presents a distinct advantage.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings, wherein like numerals designate like parts throughout the same:

FIG. **1** is a schematic flow diagram illustrating the steps of the process of the invention;

FIG. **2** represents a release profile for a multi-layer system showing the percentage of heparin released over a two-week period;

FIG. **3** represents a release profile for a multi-layer system showing the relative release rate of heparin over a two-week period;

FIG. **4** illustrates a profile of release kinetics for different drug loadings at similar coating thicknesses illustrating the release of heparin over a two-week period without associated means to provide a long term non-thrombogenic surface thereafter;

FIG. **5** illustrates drug elution kinetics at a given loading of heparin over a two-week period at different coating thicknesses without associated means to provide a long term non-thrombogenic surface thereafter;

FIG. **6** illustrates the release kinetics for a given undercoat and topcoat material varied according to thickness in which the percentage heparin in the undercoat and topcoats are kept constant;

FIG. **7** is a plot of heparin release kinetics in phosphate buffer system at PH 7.4 with and without fluorosilicone (FSi) topcoat; and

FIG. **8** is another plot of heparin release kinetics in phosphate buffer system in which a topcoat containing fluorosilicone (FSi) only is compared with an FSi topcoat containing 16.7% imbedded heparin.

DETAILED DESCRIPTION

According to the present invention, the stent coatings incorporating biologically active materials for timed delivery in situ in a body lumen of interest are preferably sprayed in many thin layers from prepared coating solutions or suspensions. The steps of the process are illustrated generally in FIG. **1**. The coating solutions or suspensions are prepared at **10** as will be described later. The desired amount of crosslinking agent (if any) is added to the suspension/solution as at **12** and material is then agitated or stirred to produce a homogenous coating composition at **14** which is thereafter transferred to an application container or device which may be a container for spray painting at **16**. Typical exemplary preparations of coating solutions that were used for heparin and dexamethasone appear next.

General Preparation of Heparin Undercoating Composition

Silicone was obtained as a polymer precursor in solvent (xylene) mixture. For example, a 35% solid silicone weight content in xylene was procured from Applied Silicone, Part #40,000. First, the silicone-xylene mixture was weighed. The solid silicone content was determined according to the vendor's analysis. Precalculated amounts of finely divided heparin (2–6 microns) were added into the silicone, then tetrahydrofuron (THF) HPCL grade (Aldrich or EM) was added. For a 37.5% heparin coating, for example: $W_{silicone}$=5 g; solid percent=35%; W_{hep}=5×0.35×0.375/(0.625)=1.05 g. The amount of THF needed (44 ml) in the coating solution was calculated by using the equation $W_{silicone\ solid}/V_{THF}$=0.04 for a 37.5% heparin coating solution). Finally, the manufacturer crosslinker solution was added by using Pasteur P-pipet. The amount of crosslinker added was formed to effect the release rate profile. Typically, five drops of crosslinker solution were added for each five grams of silicone-xylene mixture. The solution was stirred by using the stirring rod until the suspension was homogenous and milk-like. The coating solution was then transferred into a paint jar in condition for application by air brush.

General Preparation of Dexamethasone Undercoating Composition

Silicone (35% solution as above) was weighed into a beaker on a Metler balance. The weight of dexamethasone free alcohol or acetate form was calculated by silicone weight multiplied by 0.35 and the desired percentage of dexamethasone (1 to 40%) and the required amount was then weighed. Example: $W_{silicone}$=5 g; for a 10% dexamethasone coating, W_{dex}=5×0.35×0.1/0.9=0.194 g and THF needed in the coating solution calculated. $W_{silicone\ solid}/V_{THF}$=0.06 for a 10% dexamethasone coating solution. Example: $W_{silicone}$=5 g; V_{THF}=5×0.35/0.06≈29 ml. The dexamethasone was weighed in a beaker on an analytical balance and half the total amount of THF was added. The solution was stirred well to ensure full dissolution of the dexamethasone. The stirred DEX-THF solution was then transferred to the silicone container. The beaker was washed with the remaining THF and this was transferred to the silicone container. The crosslinker was added by using a Pasteur pipet. Typically, five drops of crosslinker were used for five grams of silicone.

The application of the coating material to the stent was quite similar for all of the materials and the same for the heparin and dexamethasone suspensions prepared as in the above Examples. The suspension to be applied was transferred to an application device, at **16** in FIG. **1**. Typically a paint jar attached to an air brush, such as a Badger Model 150, supplied with a source of pressurized air through a regulator (Norgren, 0–160 psi) was used. Once the brush hose was attached to the source of compressed air downstream of the regulator, the air was applied. The pressure was adjusted to approximately 15–25 psi and the nozzle condition checked by depressing the trigger.

Any appropriate method can be used to secure the stent for spraying and rotating fixtures were utilized successfully in the laboratory. Both ends of the relaxed stent were fastened to the fixture by two resilient retainers, commonly alligator clips, with the distance between the clips adjusted so that the stent remained in a relaxed, unstretched condition. The rotor was then energized and the spin speed adjusted to the desired coating speed, nominally about 40 rpm.

With the stent rotating in a substantially horizontal plane, the spray nozzle was adjusted so that the distance from the nozzle to the stent was about 2–4 inches and the composition was sprayed substantially horizontally with the brush being directed along the stent from the distal end of the stent to the proximal end and then from the proximal end to the distal end in a sweeping motion at a speed such that one spray cycle occurred in about three stent rotations. Typically a pause of less than one minute, normally about one-half minute, elapsed between layers. Of course, the number of coating layers did and will vary with the particular application. For example, typical tie-layers as at **18** in FIG. **1**, for a coating level of 3–4 mg of heparin per cm^2 of projected area, 20 cycles of coating application are required and about 30 ml of solution will be consumed for a 3.5 mm diameter by 14.5 cm long stent.

The rotation speed of the motor, of course, can be adjusted as can the viscosity of the composition and the flow rate of the spray nozzle as desired to modify the layered structure. Generally, with the above mixes, the best results have been obtained at rotational speeds in the range of 30–50 rpm and with a spray nozzle flow rate in the range of 4–10 ml of coating composition per minute, depending on the stent size. It is contemplated that a more sophisticated, computer-controlled coating apparatus will successfully automate the process demonstrated as feasible in the laboratory.

Several applied layers make up what is called the undercoat as at **18**. In one process, additional upper undercoat

layers, which may be of the same or different composition with respect to bioactive material, the matrix polymeric materials and crosslinking agent, for example, may be applied as the top layer as at **20**. The application of the top layer follows the same coating procedure as the undercoat with the number and thickness of layers being optional. Of course, the thickness of any layer can be adjusted by adjusting the speed of rotation of the stent and the spraying conditions. Generally, the total coating thickness is controlled by the number of spraying cycles or thin coats which make up the total coat.

As shown at **22** in FIG. **1**, the coated stent is thereafter subjected to a curing step in which the pre-polymer and crosslinking agents cooperate to produce a cured polymer matrix containing the biologically active species. The curing process involves evaporation of the solvent xylene, THF, etc. and the curing and crosslinking of the polymer. Certain silicone materials can be cured at relatively low temperatures, (i.e. RT-50° C.) in what is known as a room temperature vulcanization (RTV) process. More typically, however, the curing process involves higher temperature curing materials and the coated stents are put into an oven at approximately 90° C. or higher for approximately 16 hours. The temperature may be raised to as high as 150° C. for dexemethasane containing coated stents. Of course, the time and temperature may vary with particular silicones, crosslinkers and biologically active species.

Stents coated and cured in the manner described need to be sterilized prior to packaging for future implantation. For sterilization, gamma radiation is a preferred method particularly for heparin containing coatings; however, it has been found that stents coated and cured according to the process of the invention subjected to gamma sterilization may be too slow to recover their original posture when delivered to a vascular or other lumen site using a catheter unless a pretreatment step as at **24** is first applied to the coated, cured stent.

The pretreatment step involves an argon plasma treatment of the coated, cured stents in the unconstrained configuration. In accordance with this procedure, the stents are placed in a chamber of a plasma surface treatment system such as a Plasma Science 350 (Himont/Plasma Science, Foster City, Calif.). The system is equipped with a reactor chamber and RF solid-state generator operating at 13.56 mHz and from 0–500 watts power output and being equipped with a microprocessor controlled system and a complete vacuum pump package. The reaction chamber contains an unimpeded work volume of 16.75 inches (42.55 cm) by 13.5 inches (34.3 cm) by 17.5 inches (44.45 cm) in depth.

In the plasma process, unconstrained coated stents are placed in a reactor chamber and the system is purged with nitrogen and a vacuum applied to 20–50 mTorr. Thereafter, inert gas (argon, helium or mixture of them) is admitted to the reaction chamber for the plasma treatment. A highly preferred method of operation consists of using argon gas, operating at a power range from 200 to 400 watts, a flow rate of 150–650 standard ml per minute, which is equivalent to 100–450 mTorr, and an exposure time from 30 seconds to about 5 minutes. The stents can be removed immediately after the plasma treatment or remain in the argon atmosphere for an additional period of time, typically five minutes.

After this, as shown at **26**, the stents may be exposed to gamma sterilization at 2.5–3.5 Mrad. The radiation may be carried out with the stent in either the radially nonconstrained status—or in the radially constrained status.

Preferably, however, the surface is modified prior to plasma treatment or just prior to sterilization by one of several additional processing methods of which some are described in relation to the following examples.

EXAMPLE 1

Fluorosilicone Surface Treatment of Eluting Heparin Coating

The undercoat of a stent was coated as multiple applied layers as described above thereafter and cured as described at **22**. The heparin content of the undercoat was 37.5% and the coating thickness was about 30–40μ. Fluorosilicone (FSi) spray solution was prepared at **30** from a fluorosilicone suspension (Applied Silicone #40032) by weighing an amount of fluorosilicone suspension and adding tetrahydrofuran (THF) according to the relation equation of V_{THF}= 1.2xthe weight of fluorosilicone suspension. The solution was stirred very well and spray-coated on the stent at **32** using the technique of the application of the undercoat process at **18** and the coated stents were cured at 90° C. for 16 hours. The coated stents are argon plasma treated prior to gamma sterilization according to the procedures described above in accordance with steps 22–26.

FIG. **7** is a plot of heparin release kinetics in phosphate buffer system with fluorosilicone topcoat and without any topcoat. The thickness of the topcoat is about 10–15μ. While it does not appear on the graph of FIG. **7**, it should be noted that the release rate for the coating without FSi is initially about 25 times higher than that with FSi, i.e., during the first 2 hours. This is, of course, clearly off the scale of the graph. It is noteworthy, however, that the coating with the FSi top layer or diffusion barrier does show a depressed initial release rate combined with an enhanced elusion rate after the first day and through the first week up until about the tenth day. In addition, the fluorosilicone (FSi) topcoat, by virtue of the high electro-negativity of fluorination maintains non-thrombogenic surface qualities during and after the elusion of the biologically active heparin species. In addition, because of the negative charges on the heparin itself, the electro-negativity of the fluorosilicone topcoat may be, at least in part, responsible for the modified heparin release kinetic profile.

FIG. **8** compares a plot of fluorosilicone (FSi) top coating containing 16.7% imbedded heparin with one containing fluorosilicone (FSi) only. An undercoating is identical to that utilized in FIG. **7** containing about 37.5% heparin to a thickness of about 30–40 microns. These elution kinetics are quite comparable with the heparin-free FSi top layer greatly reducing the initial burst of heparin release and otherwise the heparin in the FSi top layer imparts a slightly greater release over the period of the test.

EXAMPLE 2

Immobilization of Polyethylene Glycol (PEG) on Drug Eluting Undercoat

An undercoat was coated on a stent and cured at **22** as in Example 1. The stent was then treated by argon gas plasma as at **24** and ammonium gas plasma at **40**. The equipment and the process of argon gas plasma treatment was as has been described above. The ammonium plasma treatment was implemented immediately after the argon gas plasma treatment, to aminate the surface of the coating. The ammonium flow rate was in the range of 100–700 cubic centimeter per minute (ccM) in preferably in the range of 500–600 ccM. The power output of radio frequency plasma was in the range of 50–500 watts, preferably in ~200 watts. The process time was in the range of 30 sec–10 min, preferably ~5 min.

Immediately after amination, the stents were immersed into electrophilically activated polyethylene glycol (PEG)

solution at 42. PEG is known to be an inhibitor of protein absorption. Examples of electrophilically activated PEG are PEG nitrophenyl carbonates, PEG trichlorophenyl carbonates, PEG tresylate, PEG glycidyl ether, PEG isocyanate, etc., optionally with one end terminated with methoxyl group. Molecular weight of PEG ranged from about 1000–6000, and is preferable about 3000. It has been observed that simple ammonium amination will not generate large quantities of primary and secondary amines on the elastomeric polymer surface (for example silicone). Instead, imine (>C=N—H), and other more oxidative nitro containing groups will dominate the surface. It is generally necessary to add reductive agent such as $NaBH_3CN$ into the reaction media so that the functional group on PEG can react with imine and possibly other nitro-containing species on the surface, and therefore immobilize PEG onto the surface. The typical concentration of $NaBH_3CN$ is about 2 mg/ml. Since PEG and its derivatives dissolve in water and many polar and aromatic solvents, the solvent used in the coating must be a solvent for PEG but not for the drug in the undercoat to prevent the possible loss of the drug through leaching. In the case of eluting-heparin coating, a mixed solvent of formamide and methyl ethyl ketone (MEK) or a mixed solvent of formamide and acetone are preferred solvents (preferably at ratios of 30 formamide: 70 MEK or acetone by volume), since they will not dissolve heparin. The concentration of PEG, the reaction time, the reaction temperature and the pH value depend on the kind of PEG employed. In the case of eluting heparin coating, 5% PEG tresylate in (30–70) Formamide/MEK was used successfully. The reaction time was 3 hours at room temperature. PEG was then covalently bound to the surface. Gamma radiation was then used for sterilization of this embodiment as previously described.

With respect to the anticoagulant material heparin, the percentage in the undercoat is nominally from about 30–50% and that of the topcoat from about 0–30% active material. The coating thickness ratio of the topcoat to the undercoat varies from about 1:10 to 1:2 and is preferably in the range of from about 1:6 to 1:3.

Suppressing the burst effect also enables a reduction in the drug loading or in other words, allows a reduction in the coating thickness, since the physician will give a bolus injection of antiplatelet/anticoagulation drugs to the patient during the stenting process. As a result, the drug imbedded in the stent can be fully used without waste. Tailoring the first day release, but maximizing second day and third day release at the thinnest possible coating configuration will reduce the acute or subacute thrombosis.

FIG. 4 depicts the general effect of drug loading for coatings of similar thickness. The initial elution rate increases with the drug loading as shown in FIG. 5. The release rate also increases with the thickness of the coating at the same loading but tends to be inversely proportional to the thickness of the topcoat as shown by the same drug loading and similar undercoat thickness in FIG. 6.

What is apparent from the data gathered to date, however, is that the process of the present invention enables the drug elution kinetics to be controlled in a manner desired to meet the needs of the particular stent application. In a similar manner, stent coatings can be prepared using a combination of two or more drugs and the drug release sequence and rate controlled. For example, antiproliferation drugs may be combined in the undercoat and antiplatelet drugs in the topcoat. In this manner, the antiplatelet drugs, for example, heparin, will elute first followed by antiproliferation drugs to better enable safe encapsulation of the implanted stent.

The heparin concentration measurement were made utilizing a standard curve prepared by complexing azure A dye with dilute solutions of heparin. Sixteen standards were used to compile the standard curve in a well-known manner.

For the elution test, the stents were immersed in a phosphate buffer solution at pH 7.4 in an incubator at approximately 37° C. Periodic samplings of the solution were processed to determine the amount of heparin eluted. After each sampling, each stent was placed in heparin-free buffer solution.

As stated above, while the allowable loading of the elastomeric material with heparin may vary, in the case of silicone materials heparin may exceed 60% of the total weight of the layer. However, the loading generally most advantageously used is in the range from about 10% to 45% of the total weight of the layer. In the case of dexamethasone, the loading may be as high as 50% or more of the total weight of the layer but is preferably in the range of about 0.4% to 45%.

It will be appreciated that the mechanism of incorporation of the biologically active species into a thin surface coating structure applicable to a metal stent is an important aspect of the present invention. The need for relatively thick-walled polymer elution stents or any membrane overlayers associated with many prior drug elution devices is obviated, as is the need for utilizing biodegradable or reabsorbable vehicles for carrying the biologically active species. The technique clearly enables long-term delivery and minimizes interference with the independent mechanical or therapeutic benefits of the stent itself.

Coating materials are designed with a particular coating technique, coating/drug combination and drug infusion mechanism in mind. Consideration of the particular form and mechanism of release of the biologically active species in the coating allow the technique to produce superior results. In this manner, delivery of the biologically active species from the coating structure can be tailored to accommodate a variety of applications.

Whereas the above examples depict coatings having two different drug loadings or percentages of biologically active material to be released, this is by no means limiting with respect to the invention and it is contemplated that any number of layers and combinations of loadings can be employed to achieve a desired release profile. For example, gradual grading and change in the loading of the layers can be utilized in which, for example, higher loadings are used in the inner layers. Also layers can be used which have no drug loadings at all. For example, a pulsatile heparin release system may be achieved by a coating in which alternate layers containing heparin are sandwiched between unloaded layers of silicone or other materials for a portion of the coating. In other words, the invention allows untold numbers of combinations which result in a great deal of flexibility with respect to controlling the release of biologically active materials with regard to an implanted stent. Each applied layer is typically from approximately 0.5 microns to 15 microns in thickness. The total number of sprayed layers, of course, can vary widely, from less than 10 to more than 50 layers; commonly, 20 to 40 layers are included. The total thickness of the coating can also vary widely, but can generally be from about 10 to 200 microns.

Whereas the polymer of the coating may be any compatible biostable elastomeric material capable of being adhered to the stent material as a thin layer, hydrophobic materials are preferred because it has been found that the release of the biologically active species can generally be more predictably controlled with such materials. Preferred materials

include silicone rubber elastomers and biostable polyurethanes specifically.

This invention has been described herein in considerable detail in order to comply with the Patent Statutes and to provide those skilled in the art with the information needed to apply the novel principles and to construct and use embodiments of the example as required. However, it is to be understood that the invention can be carried out by specifically different devices and that various modifications can be accomplished without departing from the scope of the invention itself.

We claim:

1. A medical device having at least a portion which is implantable into the body of a patient, wherein at least a part of the device portion is metallic and at least part of the metallic device portion is covered with a coating for release of at least one biologically active material, wherein said coating comprises an undercoat comprising a hydrophobic elastomeric material incorporating an amount of biologically active material therein for timed release therefrom, and wherein said coating further comprises a topcoat which at least partially covers the undercoat, said topcoat comprising a biostable, non-thrombogenic material which provides long term non-thromobogenicity to the device portion during and after release of the biologically active material, and wherein said topcoat is substantially free of an elutable material.

2. The device of claim **1** wherein said biologically active material is heparin.

3. The device of claim **2** wherein the non-thrombogenic material is selected from the group consisting of fluorosilicone, polyethylene glycol (PEG), polysaccharides, phospholipids and combinations thereof.

4. The device of claim **3** wherein the non-thrombogenic material is fluorosilicone.

5. The device of claim **3** wherein the non-thrombogenic material is polyethylene glycol (PEG).

6. The device of claim **1** wherein the medical device is an expandable stent.

7. The device of claim **1** wherein the topcoat consists of a polymer.

8. The device of claim **6** wherein the stent comprises a tubular body having open ends and an open lattice sidewall structure and wherein the coating conforms to said sidewall structure in a manner that preserves said open lattice.

9. A stent for implantation in a vascular lumen comprising a tubular body having open ends and a sidewall and a coating on at least a part of a surface of said sidewall, said coating further comprising an undercoat comprising a hydrophobic elastomeric material incorporating an amount of finely divided heparin therein for timed release therefrom, and wherein said coating further comprises a topcoat comprising an amount of fluorosilicone which is capable of providing long term non-thrombogenicity to the surface during and after release of the biologically active material, wherein said topcoat at least partially covers the undercoat, and wherein said topcoat is substantially free of an elutable material.

10. The device of claim **9** wherein the sidewall is an open lattice structure and wherein the coating conforms to said sidewall structure in a manner that preserves said open lattice.

11. A stent for implantation in a vascular lumen comprising a tubular body having open ends and a sidewall and a coating on at least a part of the surface of said sidewall, said coating further comprising an undercoat comprising a hydrophobic elastomeric material incorporating an amount of finely divided heparin therein for timed release therefrom, and wherein said coating further comprises a topcoat comprising an amount of polyethylene glycol (PEG) which is capable of providing long term non-thrombogenicity to the surface during and after release of the biologically active material, wherein said topcoat at least partially covers the undercoat, and wherein said topcoat is substantially free of an elutable material.

12. The device of claim **11** wherein the sidewall is an open lattice structure and wherein the coating conforms to said sidewall structure in a manner that preserves said open lattice.

* * * * *

Pathophysiology of Atherosclerosis: Development, Regression, Restenosis

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There is now a very large number of patients with coronary artery disease who have also undergone percutaneous interventions such as coronary angioplasty. Atherosclerosis and restenosis are two distinct pathologic processes with different underlying pathophysiologic mechanisms, different natural histories, different clinical presentations, and treatment strategies. Management strategies to target both processes are currently poorly applied in clinical practice. The development of integrated management strategies to target atherosclerosis, as well as restenosis in the post-procedural period remains a priority.

Introduction

Atherosclerosis, the pathologic condition underlying myocardial infarction and other acute coronary syndromes, is the major cause of death in the Western world. Clinically apparent atherosclerosis takes decades to develop, beginning with cellular changes and intimal thickening, progressing to nonobstructive plaques over many years [1]. Further progression may result in severe plaques causing flow disturbance; however, in an individual with one or more severe flow-limiting plaques milder nonobstructive, and hence asymptomatic, plaques are widespread. Although these severe plaques focus attention by causing angina and myocardial infarction, both nonobstructive and severe plaques are subject to episodic constriction, erosion, rupture, and thrombosis, and hence may cause clinical syndromes. In fact, as nonobstructive lesions are more frequent they also more commonly underlie acute ischemic syndromes [2,3].

The management of severe, obstructive plaques has increasingly come to involve the use of percutaneous coronary intervention procedures. As many as 800,000 coronary interventions are currently performed in the United States of America each year and the application of these procedures is increasing annually [4]. These procedures are effective at providing relief from angina, and allowing early restoration of activity, although their effect on long-term outcome is not known [5]. Coronary interventions however, only address one, two, or perhaps three arterial segments and are followed by the development of restenosis, which has a characteristic pathology and natural history [6].

There is now a very large number of patients with coronary artery disease who have also undergone percutaneous interventions such as coronary angioplasty, and who require follow-up. These patients now have two disease processes, their coronary artery disease, and restenosis of the treated arterial segment. These are two distinct pathologic processes with different underlying pathophysiologic mechanisms, different natural histories, different clinical presentations, and treatment strategies. This review will discuss the pathologic processes, development of clinical syndromes, and treatment strategies in atherosclerosis and restenosis. These processes are very different, and the treatment strategies required are very different. Optimal management of both the arterial segment that has undergone interventional treatment, as well as the widespread process of atherosclerosis is currently poorly applied in clinical practice [7,8,9••]. The development of integrated management strategies to target atherosclerosis, as well as restenosis in the postprocedural period remains a priority.

Pathogenesis of Atherosclerosis

The development of atherosclerosis is complex, involving the interaction of a variety of cells and molecules. Risk factors such as oxidized low-density lipoprotein (LDL), and shear forces outside the normal range may be toxic influences and activate genes of cells within conduit arteries (*eg*, endothelial and smooth muscle cells). These factors may also activate genes and increase the activity of mRNA in circulating blood cells (*eg*, monocytes, T lymphocytes, and platelets) [1,10].

There is upregulation of the genes coding for the enzymes and pathways that metabolize or otherwise handle oxidized LDL and other atherogenic factors, leading to the increased expression of xanthine oxidase, glutathione reductase, catalase, and nicotinamide adenine dinucleotide phosphate (NADPH), amongst others. There is upregulation of

amplifiers of these pathways and the production of chronic inflammation through the activation of NF-kB and protein kinase C, and the production of cell adhesion molecules, ligands, and cytokines [10,11••,12,13]. This metabolic interaction and activation of cells results in the production of excess free radicals, endothelial dysfunction, chronic low-grade inflammation and the promotion of thrombosis, ultimately resulting in an activated and dysfunctional artery.

Endothelial dysfunction

The endothelium performs a wide range of functions; it controls vascular tone, growth, and permeability, as well as defensive processes such as control of thrombosis and inflammation during hemostasis and repair. As a result endothelial dysfunction may initiate a series of cellular interactions involving leukocytes, platelets, and other cells, culminating in atherosclerosis. A number of insults may be responsible for endothelial injury such as increased shear stress, homocysteine, inflammatory cytokines, free radicals, and other chemicals. One of the earliest signs of endothelial injury may be the reduced production of nitric oxide [14]. This is particularly important due to the central role nitric oxide plays in inhibiting many atherogenic processes. Nitric oxide is secreted continuously by normal endothelial cells causing vasorelaxation, inhibiting cellular growth, and division, modulating inflammation, and helping to regulate thrombosis by reducing platelet aggregation and adhesion [15–17].

Oxidized low-density lipoprotein is formed by the endothelium and macrophages from native low-density lipoprotein and has a number of deleterious effects on the endothelium and other cells. Small dense LDL particles are particularly susceptible to the process of oxidative modification, which may be potentiated by a number of factors including cigarette smoke and diabetes [18]. Toxic products of lipid oxidation (*eg*, reactive hydroxyfatty acids and lysophosphotidylcholine) may accumulate and apolipoprotein-B may be oxidatively modified, preventing normal binding to the native LDL receptor [19].

One of the major effects of oxidized LDL is an impairment of the endothelial production of nitric oxide. This results from direct inactivation of NO by superoxide anions, and production of toxic compounds (*eg*, peroxinitrous acid) as well as a reduction in nitric oxide production [20]. On exposure to oxidized LDL, there is a dramatic decrease in nitric oxide synthase activity in endothelial cells. This occurs due to the direct action of oxidized LDL on DNA for nitric oxide synthase, the activation of protein kinase C, disturbance of intracellular signal transduction, inhibition of transcription of this enzyme, destabilization of post-transcriptional mRNA, and production of competitive inhibitors of nitric oxide synthase [21].

Monocytes and inflammation

Monocyte adhesion to the endothelium is largely controlled by the modulation of endothelial cell adhesion molecules, such as intracellular adhension molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), although alterations in the integrins LFA-1, Mac-1 and L-selectin on the surface of human monocytes have been implicated in the development of atheroma [22]. In the subintimal space macrophages internalize oxidized low-density lipoprotein via both scavenger pathways and an oxidized low-density lipoprotein receptor [23].

Macrophages also play an important role in atherogenesis by their secretion of a number of factors in response to free radicals, oxidized LDL, and other risk factors that activate the inflammatory response through stimulation of NF-kB. For example growth factors (*eg*, platelet derived growth factor, interleukin-1, tumor necrosis factor-a, basic fibroblast growth factor, vascular endothelial cell growth factor, transforming growth factor-β) and chemotactic factors (*eg*, monocyte chemotactic protein-1, colony stimulating factors, transforming growth factor-β) amplify the inflammatory process and contribute to the proliferation of macrophages and smooth muscle cells [1,10].

Platelets and thrombosis

Platelets are normally prevented from adhering to the vessel wall by endothelial cells; however, in certain situations such as endothelial dysfunction or deendothelialization with exposure of connective tissue to the vessel lumen, platelets may be activated [24]. Platelets produce a number of important mitogenic factors including platelet-derived growth factor (PDGF), epidermal growth factor, insulin-like growth factor (IGF), and transforming growth factor-β (TGF-β), as well as a number of chemotactic agents such as thromboxane [1,25].

Platelets may also be activated by a variety of other factors, such as hypercholesterolemia and cigarette smoke [26]. In particular, oxidized LDL is a potent stimulus for platelet aggregation and thrombosis. Oxidized LDL alters the balance of various endothelial products (*eg*, nitric oxide, prostacyclin, heparan sulfate proteoglycans, and endothelin) to increase aggregation [27]. An increase in levels of plasminogen activator inhibitor and decrease in thrombomodulin and plasminogen activator, also promote local thrombosis [28].

Smooth muscle cells and atherogenesis

Smooth muscle cells are found in early fatty streaks and are the predominant cell type in established fibrous plaques. They contribute to fibrous plaques through proliferation, migration into the subintimal space, and the production of connective tissue matrix. Smooth muscle cells may also express a receptor for low-density lipoproteins leading to the accumulation of lipid and the formation of cells resembling foam cells [1]. The balance of smooth muscle cell proliferation and production of extracellular matrix plays an important role in the development of ischemic syndromes, as well as neointimal proliferation following coronary interventions [29].

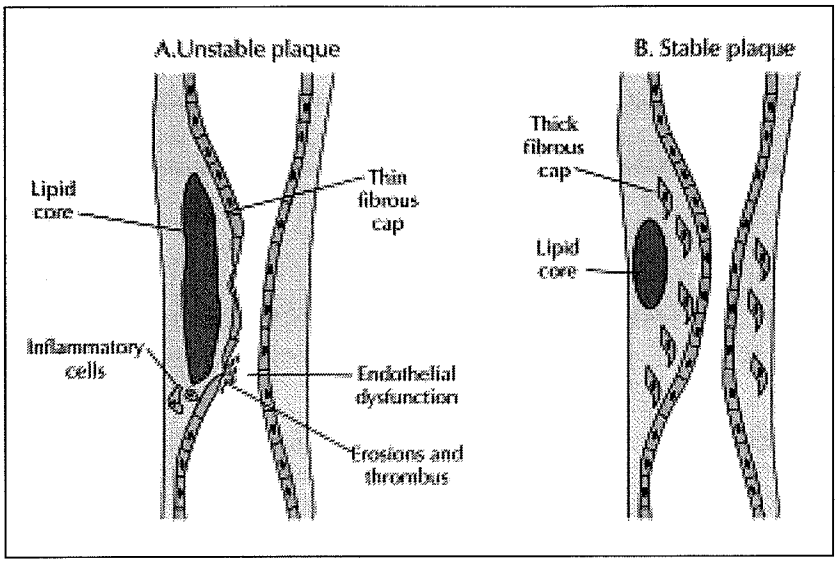

Figure 1. Stable and unstable plaques. **A,** Unstable plaques are characterized by a lipid core covered by a relatively thin fibrous cap containing less extracellular matrix and vascular smooth muscle cells, often with inflammatory cells and secretion of proteinases. This may lead to plaque fissure or rupture thus exposing lipid and tissue factor to the blood and promoting thrombosis. **B,** Stable plaques have a thicker fibrous cap with greater numbers of smooth muscle cells and extracellular matrix, and are thus less prone to fissure or rupture.

Ischemic Syndromes: Stable and Unstable Plaques

Atherosclerosis has a long natural history, with the development of atherosclerotic plaques starting decades before the development of clinical syndromes. Due to arterial remodeling (compensatory enlargement of the whole artery), a large plaque burden may be present long before there is any encroachment upon the vascular lumen [30]. Chronic ischemic syndromes (*eg*, stable angina pectoris) most often develop once plaque develops to such an extent that it limits the regulation of regional coronary blood flow. In the majority of such cases the atherosclerotic plaques responsible are usually stable and not prone to thrombosis [3]. The development of an acute coronary syndrome however, may occur independent of the hemodynamic significance of the underlying plaque, and involves quite different pathology [2,3] (Fig. 1).

Unstable atherosclerotic plaques are characteristically prone to rupture and fissuring of the surface of the plaque, thus exposing the lipid core to the circulating blood. This lipid core is rich in tissue factor, and promotes thrombosis within the vessel lumen leading to the clinical manifestations of unstable angina and myocardial infarction [3]. Rupture of vulnerable plaques usually occurs at the edges of the fibrous cap where mechanical stress is the greatest [31]. A number of factors are involved in the weakening of the fibrous cap. Macrophages, foam cells, and other leukocytes produce digestive enzymes (*eg*, metalloproteinases) that decrease the structural integrity of the fibrous cap. This process is exacerbated by the other inflammatory cells, the loss of normal endothelial function, and other risk factors. In particular, oxidized LDL is known to increase inflammation and to stimulate production of certain metalloproteinases [32]. Oxidized LDL plays an additional role by activating platelet aggregation and thrombosis, as well as decreasing fibrinolysis, and contributing to endothelial dysfunction [27]. Unstable plaques are also associated with a reduction in the number and activity of vascular smooth muscle cells, and reduced or abnormal extracellular matrix proteins, perhaps secondary to stimuli such as interferon-g secreted by T-lymphocytes [2,29].

Stable atherosclerotic plaques are characterized by a thicker layer of fibrous tissue, which protects the plaque from rupture, and a plaque characterized by cellular and extracellular matrix proliferation. In this case, smooth muscle cell activity and proliferation is protective rather than deleterious as it might be in the early process of atherogenesis [31]. However, although such plaques may be clinically stable, they may also be quite dynamic. For example, the endothelial layer covering such plaques may be dysfunctional resulting in vasoconstriction in response to increased flow rather than physiologic dilation or reduced vasodilation [33].

Restenosis: Intimal Growth and Arterial Shrinkage

Like atherosclerosis, restenosis results in a reduction in arterial lumen diameter; however, the pathologic process involved is distinctly different. Whereas symptomatic atherosclerosis often takes decades to develop, restenosis develops over a period of months, and although atherosclerotic plaques remain dynamic, the tissue in restenotic arteries becomes less active after 6 to 9 months [6]. In fact, following balloon angioplasty of unstable plaques, the plaque is generally rendered stable, even though a significant stenosis may recur at that site (29). Following arterial injury, there are several identifiable stages in the process of

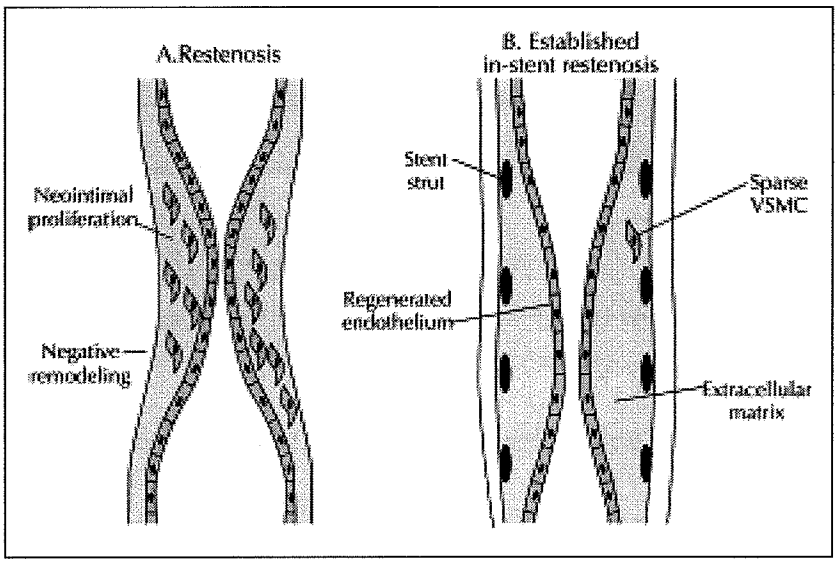

Figure 2. Restenosis following balloon angioplasty and following stent placement. **A,** Restenosis following balloon angioplasty results from a combination of neointimal proliferation, due to early vascular smooth muscle cell growth (VSMC) and deposition of extracellular matrix, and negative remodeling of the arterial wall, producing a smaller arterial diameter. **B,** In the case of in-stent restenosis negative remodeling of the artery is not a factor; however, early changes involving inflammatory cells, thrombosis, and vascular smooth muscle cell (VSMC) migration may lead to excessive production of extracellular matrix with relatively few cells and a high tensile strength.

restenosis. Immediately following angioplasty, there is a removal of endothelial cells at the site of injury and an accumulation of platelets, thrombus, and inflammatory cells. Under the influence of these as well as other factors, there is a period of cellular proliferation and migration into the area that occurs from about the second or third day. This cellular phase is the beginning of neointimal proliferation, and involves inflammatory cells as well as vascular smooth muscle cells [34]. There is growing evidence that the majority of this growth occurs within the first 2 weeks following injury, as the number of cells seems to remain constant after this period [29]. Over the following months, there is growth of the neointima due to extracellular matix formation, and there is negative remodeling of arterial size (Fig. 2). It is largely a combination of these two processes that leads to the problem of restenosis, although the relative contribution of these two mechanisms varies between individuals.

Neointimal hyperplasia

Neointimal hyperplasia occurs under the influence of a variety of factors and ultimately results from the proliferation and migration of vascular smooth muscle cells, as well as the elaboration of extracellular matrix. There is evidence that the degree of neointimal hyperplasia that occurs after balloon angioplasty is proportional to the degree of injury delivered to the arterial wall [35]. Prevention of vascular smooth muscle cell proliferation, growth and differentiation has become the major target for therapies aimed at preventing restenosis.

The growth and differentiation of vascular smooth muscle cells is normally tightly regulated in healthy arteries. In atherosclerotic plaques, there may be some deregulation of smooth muscle cell growth, although this may also be inhibited in the setting of an unstable plaque. Balloon angioplasty results in the denudation of endothelial cells at the site of injury, and its replacement by platelets and thrombus. In turn this results in the recruitment of inflammatory cells. Smooth muscle cell growth is normally inhibited by endothelial products such as proteoglycans and nitric oxide, the loss of which stimulates cellular growth [34,35] (Fig. 3). One determinant of the degree of proliferation that occurs, is the time it takes for reestablishment of normal endothelial function [36]. The deposition of platelets results in the release of powerful factors that induce cell division, migration, and differentiation, including platelet-derived growth factor (PDGF), thromboxane A2, and transforming growth factor-β (TGF-β) [37]. Direct damage of the vessel may result in increased oxidative stress within the vessel wall leading to activation of multifunctional transcription factor NF-κβ, as well as genes controlling cellular growth [11,38]. Injury to the smooth muscle cell itself similarly may activate cellular proliferation both directly and by smooth muscle cell production of mitogens and cytokines, such as tumor necrosis factor-α (TNF-α), insulin-like growth factor-1 (IGF-1), basic fibroblast growth factor (bFGF), and angiotensin II [37].

Inflammatory cells play an important role in this cellular proliferation within the intimal space. Leukocytes enter the area, facilitated by the loss of endothelium, the presence of thrombin and the secretion of cytokines. In addition, activated smooth muscle cells produce intracellular adhesion molecules such as ICAM-1 on their surface, further attracting monocytes [39]. The production of ICAM-1 and the interaction with monocytes appear to be important steps. Experimental studies have demonstrated blocking ICAM-1 reduces neointimal hyperplasia, and that neointimal production is markedly reduced in Mac-1 deficient mice [40]. Monocytes produce a number of cytokines including platelet-derived growth factor (PDGF), interleukin-1, interleukin-6, basic fibroblast growth factor (bFGF), tumor necrosis factor-α (TNF-αII, and transforming growth factor-β (TGF-β) [37].

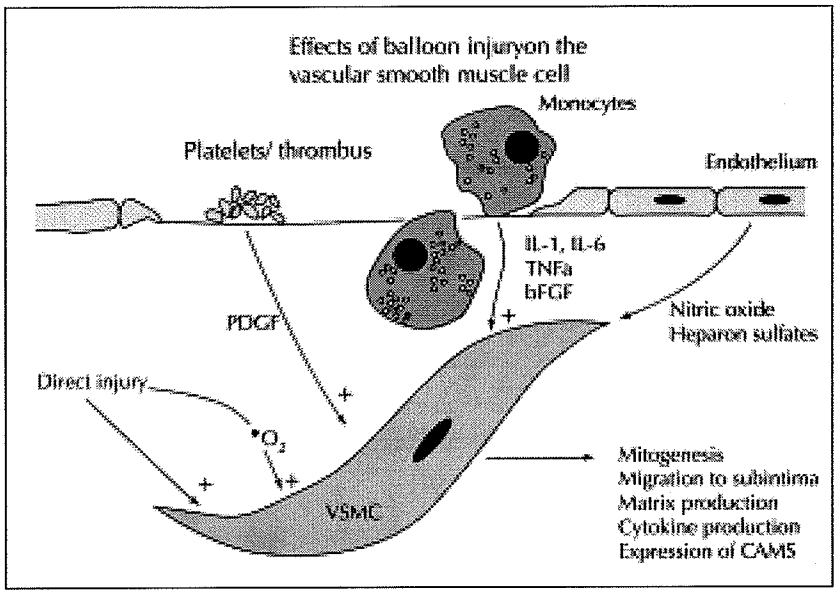

Figure 3. Effects of balloon injury on the vascular smooth muscle cell. Following balloon angioplasty the treated area of the artery is deendothelialized, thus altering important regulatory stimuli such as nitric oxide and heparan sulfates which inhibit vascular smooth muscle cells (VSMC). In addition, the deposition of thrombus and platelets on the lumenal surface attracts inflammatory cells, and platelets produce platelet-derived growth factor (PDGF) that stimulates VSMC. Inflammatory cells produce a number of cytokines that stimulate VSMC including interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-a (TNF-a), and basic fibroblast growth factor (bFGF). The balloon injury itself stimulates the VSMC directly and via the production of free radicals (O^{2-}). Activation of VSMCs results in proliferation, migration, production of extracellular matrix, and cytokines and expression of cell adhesion molecules (CAMs).

A variety of intracellular signals such as cyclic AMP, protein kinase C, protein kinase A, and calcium mediate the effect of these mitogens and cytokines in the activation of gene expression and the entry of the vascular smooth muscle cell into the proliferation stage of the cell cycle [41]. The stimulation of vascular smooth muscle growth therefore occurs due to a large number of complex and redundant stimuli, from a variety of sources culminating in the deregulation of cell growth and proliferation. For example, both bFGF and PDGF are able to facilitate the transcription of the proto-oncogenes c-Fos and c-myc, allowing initiation of the cell cycle [42].

The extracellular matrix is an active participant in the development of the neointima. In the first 3 to 4 weeks of restenosis, the thrombus covering the arterial surface is replaced by hyaluronic acid and glycoproteins; however, after this time there is a gradual deposition of collagen and elastin, resulting in a neointimal growth with high tensile strength [43]. Hyaluronic acid as well as glycoproteins (*eg*, osteopontin and fibronectin) play an important part in the migration of smooth muscle cells into the subintima involving a number of specific smooth muscle cell integrins. For example, the interactions between the smooth muscle cell integrin CD44 and hyaluronic acid, and between the avb3 integrin and osteopontin seem to be important in smooth muscle cell migration. More information is required however, to fully elucidate these interactions.

Arterial remodeling and vascular stents

Neointimal hyperplasia is not the sole factor in the development of restenosis. Some animal models of vessel injury have in fact found negative remodeling of the artery to be the dominant cause of restenosis [44]. Human studies utilizing intravascular ultrasound, after vascular injury have demonstrated that arterial remodeling occurs in addition to neointimal growth, and similar results have been found in autopsy studies. These studies have found the degree of neointimal growth to be correlated with vessel size, and the development of restenosis dependent on what type of remodeling occurs. If remodeling increases arterial size to accommodate the formation of neointima, there is no reduction in lumen area; however, unfavorable geometric remodeling will result in a reduction in arterial size and lumenal restenosis [44].

The process responsible for remodeling involves smooth muscle cell growth and apoptosis within the media and adventitia of the artery. The production of extracellular matrix and its modification (*eg*, cross-linking of collagen) are involved, as are various proteases produced in the vessel wall [29,44]. These changes occur under the influence of growth factors produced within the vessel wall, external hemodynamic influences, and other vasoactive substances (*eg*, nitric oxide) [45]. The determinants of favorable or unfavorable remodeling are as yet not clear, although there is some evidence that the unfavorable remodeling may be associated with greater adventitial damage [44].

The use of endovascular stents in interventional cardiology has become widespread in the last 5 years, with approximately 500,000 patients having stents implanted in 1998 [4]. The use of stents has basically removed the issue of unfavorable vessel remodeling. Although in many cases this has reduced the incidence of restenosis, it has not removed the problem altogether. The occurrence of in-stent restenosis is a function of vessel size, it is uncommon in large vessels, but occurs commonly in small caliber arteries [4]. The pathology of this process is similar to that of restenosis, although almost all of the lumen loss is secondary to excessive neointimal hyperplasia. The process of in-stent restenosis is predominated by more extensive covering of the area with thrombus, a greater inflammatory response, and more rapid prolifera-

tion of smooth muscle cells at an early stage, which is later marked by large production of extracellular matrix with few smooth muscle cells [46] (Fig. 2). The degree of smooth muscle cell hyperplasia and inflammation may be related to the amount of deep vascular damage at stent deployment and the presence of foreign material within the arterial wall [36,47].

Management of Coronary Artery Disease: Restenosis and Plaque Regression

The management of coronary artery disease aims to improve clinical outcomes and requires an integrated approach to deal with the spectrum of disease ranging through acute coronary syndromes, the problem of postintervention restenosis and the long-term management aimed at plaque stabilization and regression.

Plaque stabilization and regression

Numerous experimental and clinical studies have shown that the structural regression of atherosclerotic plaque may be feasible both in animal models and in humans. During regression of atherosclerotic plaque, certain structural changes seem to occur. Importantly there is evidence that atherosclerotic plaques can stabilize during the regression process, becoming less likely to fissure or rupture [47]. This may be due to a decrease in the lipid core or to an increase in the protective fibrous cap of the plaque. These changes might not be readily apparent on angiography or ultrasound but can occur rapidly after cholesterol lowering [48].

Lipid-lowering is associated with a pronounced and rapid improvement in vascular function. In vitro and in vivo experiments suggest that lowering cholesterol is associated with improvement in endothelial function and increased bioavailability of nitric oxide [47]. Several studies in humans have shown that cholesterol lowering may improve coronary artery endothelial function within several months, or even within hours of intervention [49]. In addition, reduction in cholesterol levels has favorable effects on reducing oxidant stress, decreasing inflammation within the vessel wall and decreasing the platelet adhesion and the thrombogenicity of blood [47].

Given the range of cellular changes induced by cholesterol lowering and the speed at which these occur, it is not surprising that controlled trials of cholesterol lowering have demonstrated a marked improvement in survival of patients with coronary artery disease, or that these changes are conferred soon after cholesterol lowering [50]. Recent evidence suggests that plaque regression by lipid lowering may be superior to revascularization by percutaneous intervention in low-risk patients with stable ischemic syndromes. For example, Pitt *et al.* [51••] studied over 300 patients randomized to intervention or aggressive lipid lowering, and found no difference in survival, but a decreased incidence of recurrent ischemic events with lipid lowering. Cholesterol lowering following acute coronary events has been shown to improve endothelial function [52]. The rapid nature of many of the cellular and molecular changes that occur with aggressive cholesterol lowering suggest that this may also be of use in the treatment of acute coronary syndromes, although this requires further investigation.

Prevention of restenosis postcoronary intervention

At present, percutaneous coronary intervention is a very prominent modality in the treatment of acute and stable coronary syndromes. Although the procedure is effective in the immediate control of symptoms, as yet no effective method has been found to prevent the occurrence of restenosis. Research of this area has been aided by the use of a variety of animal models, which have contributed to the understanding of this problem. However, many of the strategies that have been effective in animals have not been effective in humans, most likely due to differences in the experimental models, and the number of redundant mechanisms involved in the evolution of restenosis [35]. The majority of approaches to restenosis have centered on prevention of smooth muscle cell proliferation. Attempts to block specific stimuli to growth (*eg*, angiotensin II) have been disappointing as have the use of nitric oxide donors and antioxidants [53]. As a result, the final proliferative cell cycle has been targeted using a variety of measures such as gene transfer therapy, antisense oligodeoxynucleotides aimed at specific genes involved in cellular proliferation, cell cycle toxins, and irradiation [37]. Phosphodiesterase inhibitors have been used to inhibit cellular proliferation via the activation of a cyclic AMP-protein kinase, a signaling pathway [41]. Almost all of these above therapies have shown promise in animal models but have not yet proven feasible or effective in humans.

Several strategies have shown some beneficial effect in human trials. Firstly g-radiation has been demonstrated to reduce the incidence of restenosis, although this requires further long-term follow-up. The use of b-particle radiation also requires further evaluation [11]. The blocking of cell adhesion/migration with antagonists of certain integrins has also shown some promise [43]. In the Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial, Topol *et al.* [54] described the use of a monoclonal antibody against the β3 integrin to reduce platelet aggregation. This integrin is also involved in cell migration, and in this trial there was some reduction in the need for repeat procedures suggesting reduced restenosis. Aggressive lowering of lipoprotein (a) by apheresis has also been associated with a reduction in angiographic restenosis, possibly via improvements in fibrinolytic activity [55]. Further work is needed to evaluate these treatment strategies.

Combined management of coronary artery disease and restenosis

In postintervention management, the control of risk factors has not proven to be a useful strategy to reduce restenosis. However, there is an overwhelming body of evi-

dence that such measures are associated with improved clinical outcome [47]. Despite this, the treatment of factors such as hypercholesterolemia remain underutilized [7–9]. Recent studies have demonstrated that the use of statins is safe in the setting of acute coronary syndromes, and that many of the molecular and cellular benefits occur rapidly after this [49,52]. Serruys *et al.* [56••] recently studied the use of Fluvastatin following balloon angioplasty, and found although there was no apparent change in restenosis that there was already a survival benefit with moderate cholesterol lowering at 40 weeks postprocedure. Although the use of early aggressive cholesterol lowering requires further evaluation in acute coronary syndromes, the case for addressing all risk factors at the time of coronary intervention is impressive.

Conclusions

Atherosclerosis is a condition with a long natural history, often beginning long before the occurrence of clinical syndromes. Recent work has lead to a greater understanding of the cellular and molecular mechanisms underlying atherogenesis and the subsequent development of acute ischemic syndromes. Lipids such as oxidized LDL play a central role in both of these processes.

Contemporary treatment strategies focus on the treatment of acute coronary syndromes, often with the use of percutaneous interventions. Once patients have undergone coronary interventions, coronary arteries will be subject to two very different pathologic processes: those of diffuse coronary atherosclerosis and restenosis. Even a successful intervention however, will only improve matters in one arterial segment. Such interventions do not target the bulk of the atheromatous disease, and have not yet been shown to change the longer-term clinical outcome. Why do these patients not receive lipid-lowering therapy postintervention? The application of treatment strategies to address both pathologic processes remains a challenge for the future.

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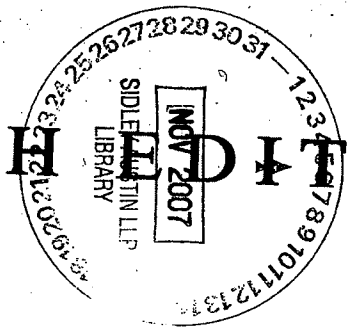

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fr. L *restaurare* to renew, rebuild, alter. of *instaurare* to renew] (14c) **1** : GIVE BACK, RETURN **2** : to put or bring back into existence or use **3** : to bring back to or put back into a former or original state : RENEW **4** : to put again in possession of something *syn* see RENEW — **re·stor·er** *n*

re·strain \ri-'strān\ *vt* [ME *restraynen*, fr. MF *restraindre*, fr. L *restringere* to restrain, restrict, fr. *re-* + *stringere* to bind tight — more at STRAIN] (14c) **1 a** : to prevent from doing, exhibiting, or expressing ⟨~*ed* the child from jumping⟩ **b** : to limit, restrict, or keep under control ⟨try to ~ your anger⟩ **2** : to moderate or limit the force, effect, development, or full exercise of ⟨~ trade⟩ **3** : to deprive of liberty; *esp* : to place under arrest or restraint — **re·strain·able** \-'strā-nə-bəl\ *adj* — **re·strain·er** *n*

syn RESTRAIN, CHECK, CURB, BRIDLE mean to hold back from or control in doing something. RESTRAIN suggests holding back by force or persuasion from acting or from going to extremes ⟨*restrained* themselves from laughing⟩. CHECK implies restraining or impeding a progress, activity, or impetus ⟨trying to *check* government spending⟩. CURB suggests an abrupt or drastic checking ⟨learn to *curb* your appetite⟩. BRIDLE implies keeping under control by subduing or holding in ⟨*bridle* an impulse to throw the book down⟩.

re·strained \ri-'strānd\ *adj* (14c) : marked by restraint : being without excess or extravagance — **re·strain·ed·ly** \-'strā-nəd-lē\ *adv*

restraining order *n* (ca. 1876) **1** : a preliminary legal order sometimes issued to keep a situation unchanged pending decision upon an application for an injunction **2** : a legal order issued against an individual to restrict or prohibit access or proximity to another specified individual

re·straint \ri-'strānt\ *n* [ME, fr. MF *restrainte*, fr. *restraindre*] (15c) **1 a** : an act of restraining : the state of being restrained **b** (1) : a means of restraining : a restraining force or influence (2) : a device that restricts movement ⟨a ~ for children riding in cars⟩ **2** : a control over the expression of one's emotions or thoughts

re·strict \ri-'strikt\ *vt* [L *restrictus*, pp. of *restringere*] (1535) **1** : to confine within bounds : RESTRAIN **2** : to place under restrictions as to use or distribution *syn* see LIMIT

re·strict·ed *adj* (ca. 1828) : subject or subjected to restriction: as **a** : not general : LIMITED ⟨the decision had a ~ effect⟩ **b** : available to the use of particular groups or specif. excluding others ⟨a ~ country club⟩ **c** : not intended for general circulation or release ⟨a ~ document⟩ — **re·strict·ed·ly** *adv*

re·stric·tion \ri-'strik-shən\ *n* [ME *restriccioun*, fr. LL *restriction-*, *restrictio*, fr. L *restringere*] (15c) **1** : something that restricts: as **a** : a regulation that restricts or restrains ⟨~s for hunters⟩ **b** : a limitation on the use or enjoyment of property or a facility **2** : an act of restricting : the condition of being restricted

restriction enzyme *n* (1965) : any of various enzymes that break DNA into fragments at specific sites in the interior of the molecule — called also *restriction endonuclease*

re·stric·tion·ism \-shə-ˌni-zəm\ *n* (1937) : a policy or philosophy favoring restriction (as of trade or immigration) — **re·stric·tion·ist** \-sh(ə-)nist\ *adj or n*

re·stric·tive \ri-'strik-tiv\ *adj* (1579) **1 a** : of or relating to restriction **b** : serving or tending to restrict ⟨~ regulations⟩ **2** : limiting the reference of a modified word or phrase **3** : prohibiting further negotiation — **restrictive** *n* — **re·stric·tive·ly** *adv* — **re·stric·tive·ness** *n*

restrictive clause *n* (ca. 1895) : a descriptive clause that is essential to the definiteness of the word it modifies (as *that you ordered* in "the book that you ordered is out of print")

re·strike \(ˌ)rē-'strīk, 'rē-ˌ\ *n* (1899) : a coin or medal struck from an original die at some time after the original issue

rest room *n* (1899) : a room or suite of rooms providing toilets and lavatories

re·struc·ture \(ˌ)rē-'strək-chər\ *vt* (1942) : to change the makeup, organization, or pattern of ~ *vi* : to restructure something

¹re·sult \ri-'zəlt\ *vi* [ME, fr. ML *resultare*, fr. L, to rebound, fr. *re-* + *saltare* to leap — more at SALTATION] (15c) **1 a** : to proceed or arise as a consequence, effect, or conclusion ⟨death ~*ed* from the disease⟩ **b** : to have an issue or result ⟨the disease ~*ed* in death⟩ **2** : REVERT 2

²result *n* (1647) **1** : something that results as a consequence, issue, or conclusion; *also* : beneficial or tangible effect : FRUIT **2** : something obtained by calculation or investigation — **re·sult·ful** \-fəl\ *adj* — **re·sult·less** \-ləs\ *adj*

³re·sul·tant \ri-'zəl-tᵊnt\ *adj* (1639) : derived from or resulting from something else — **re·sul·tant·ly** *adv*

⁴resultant *n* (1815) : something that results : OUTCOME; *specif* : the single vector that is the sum of a given set of vectors

re·sume \ri-'züm\ *vb* **re·sumed; re·sum·ing** [ME, fr. MF or L; MF *resumer*, fr. L *resumere*, fr. *re-* + *sumere* to take up, take — more at CONSUME] *vt* (15c) **1** : to assume or take again : REOCCUPY ⟨*resumed* his seat by the fire —Thomas Hardy⟩ **2** : to return to or begin again after interruption ⟨*resumed* her work⟩ **3** : to take back to oneself **4** : to pick up again **5** : REITERATE, SUMMARIZE ~ *vi* : to begin again something interrupted

ré·su·mé *or* **re·su·me** *or* **re·su·mé** \'re-zə-ˌmā, ˌre-zə-' *also* 'rā- *or* ˌrā-\ *n* [F *résumé*, fr. pp. of *résumer* to resume, summarize, fr. MF *resumer*] (1804) **1** : SUMMARY **2** : CURRICULUM VITAE

re·sump·tion \ri-'zəm(p)-shən\ *n* [ME, fr. MF or LL; MF *resomption*, fr. LL *resumption-*, *resumptio*, fr. L *resumere*] (15c) **1** : an act or instance of resuming : RECOMMENCEMENT **2** : a return to payment in specie

re·su·pi·nate \ri-'süi-pə-ˌnāt\ *adj* [L *resupinatus*, pp. of *resupinare* to bend back to a supine position, fr. *re-* + *supinus* supine] (ca. 1776) **1** : inverted in position ⟨~ orchid flowers⟩ **2** : having or being a fruiting body lying flat on the substrate with the hymenium at the periphery or over the whole surface ⟨~ fungi⟩ ⟨~ sporophores⟩

re·sur·face \(ˌ)rē-'sər-fəs\ *vt* (1894) : to provide with a new or fresh surface ~ *vi* : to come again to the surface (as of the water); *broadly* : to appear or show up again — **re·sur·fac·er** \-fə-sər\ *n*

re·surge \ri-'sərj\ *vi* **re·surged; re·surg·ing** [L *resurgere*] (1575) : to undergo a resurgence

re·sur·gence \ri-'sər-jən(t)s\ *n* (ca. 1834) : a rising again into life, activity, or prominence : RENASCENCE

re·sur·gent \-jənt\ *adj* [L *resurgent-*, *resurgens*, prp. of *resurgere*] (1808) : undergoing or tending to produce resurgence

res·ur·rect \ˌre-zə-'rekt\ *vt* [back-formation fr. *resurrection*] (1772) **1** : to raise from the dead **2** : to bring to view, attention, or use again

res·ur·rec·tion \ˌre-zə-'rek-shən\ *n* [ME, fr. LL *resurrection-*, *resurrectio* act of rising from the dead, fr. *resurgere* to rise from the dead, fr. L, to rise again, fr. *re-* + *surgere* to rise — more at SURGE] (14c) **1 a** *cap* : the rising of Christ from the dead **b** *often cap* : the rising again to life of all the human dead before the final judgment **c** : the state of one risen from the dead **2** : RESURGENCE, REVIVAL **3** *Christian Science* : a spiritualization of thought : material belief that yields to spiritual understanding — **res·ur·rec·tion·al** \-shnəl, -shə-nᵊl\ *adj*

res·ur·rec·tion·ist \-sh(ə-)nist\ *n* (1776) **1** : BODY SNATCHER **2** : one who resurrects

re·sus·ci·tate \ri-'sə-sə-ˌtāt\ *vb* **-tat·ed; -tat·ing** [L *resuscitatus*, pp. of *resuscitare* to reawaken, fr. *re-* + *suscitare* to rouse, fr. *sub-*, *sus-* up + *citare* to put in motion, stir — more at SUB-, CITE] *vt* (1532) : to revive from apparent death or from unconsciousness; *also* : REVITALIZE ~ *vi* : COME TO, REVIVE — **re·sus·ci·ta·tion** \ri-ˌsə-sə-'tā-shən, ˌrē-\ *n* — **re·sus·ci·ta·tive** \ri-'sə-sə-ˌtā-tiv\ *adj*

re·sus·ci·ta·tor \ri-'sə-sə-ˌtā-tər\ *n* (ca. 1843) : one that resuscitates; *specif* : an apparatus used to restore respiration (as to a partially asphyxiated person)

ret \'ret\ *vb* **ret·ted; ret·ting** [ME, fr. MD] *vt* (14c) : to soak (as flax) to loosen the fiber from the woody tissue ~ *vi* : to become retted

re·ta·ble \'rē-ˌtā-bəl, rē-'\ *n* [F, fr. MF, modif. of OProv *retaule*, alter. of *reretaule*, ultim. fr. L *retro-* + *tabula* board, tablet] (ca. 1823) : a raised shelf above an altar for the altar cross, the altar lights, and flowers

¹re·tail \'rē-ˌtāl, *esp for 2 also* ri-'tā(ə)l\ *vb* [ME, fr. MF *retaillier* to cut back, divide into pieces, fr. OF, fr. *re-* + *taillier* to cut — more at TAILOR] *vt* (15c) **1** : to sell in small quantities directly to the ultimate consumer **2** : TELL, RETELL ~ *vi* : to sell at retail — **re·tail·er** *n*

²re·tail \'rē-ˌtāl\ *n* (15c) : the sale of commodities or goods in small quantities to ultimate consumers; *also* : the industry of such selling — **at retail** **1** : at a retailer's price **2** : ⁴RETAIL

³re·tail \'rē-ˌtāl\ *adj* (1601) : of, relating to, or engaged in the sale of commodities at retail ⟨~ trade⟩

⁴re·tail \'rē-ˌtāl\ *adv* (1784) : in small quantities : from a retailer

re·tail·ing \'rē-ˌtā-liŋ\ *n* (14c) : the activities involved in the selling of goods to ultimate consumers for personal or household consumption

re·tain \ri-'tān\ *vt* [ME *reteinen*, *retainen*, fr. MF *retenir*, fr. L *retinēre* to hold back, keep, restrain, fr. *re-* + *tenēre* to hold — more at THIN] (15c) **1 a** : to keep in possession or use **b** : to keep in one's pay or service; *specif* : to employ by paying a retainer **c** : to keep in mind or memory : REMEMBER **2** : to hold secure or intact *syn* see KEEP

retained object *n* (ca. 1904) : an object of a verb in the predicate of a passive construction (as *me* in "a book was given me" and *book* in "I was given a book")

¹re·tain·er \ri-'tā-nər\ *n* (1540) **1 a** : a person attached or owing service to a household; *esp* : SERVANT **b** : EMPLOYEE **2** : one that retains **3** : any of various devices used for holding something

²retainer *n* [ME *reteiner* act of withholding, fr. *reteinen* + AF *-er* (as in *weyver* waiver)] (1775) **1** : the act of a client by which the services of a lawyer, counselor, or adviser are engaged **2** : a fee paid to a lawyer or professional adviser for advice or services or for a claim on services when needed

¹re·take \(ˌ)rē-'tāk\ *vt* **-took** \-'tůk\; **-tak·en** \-'tā-kən\; **-tak·ing** (15c) **1** : to take or receive again **2** : RECAPTURE **3** : to photograph again

²re·take \'rē-ˌtāk\ *n* (1916) : a subsequent filming, photographing, or recording undertaken to improve upon the first; *also* : an instance of this

re·tal·i·ate \ri-'ta-lē-ˌāt\ *vb* **-at·ed; -at·ing** [LL *retaliatus*, pp. of *retaliare*, fr. L *re-* + *talio* legal retaliation] *vt* (1611) : to repay (as an injury) in kind ~ *vi* : to return like for like; *esp* : to get revenge *syn* see RECIPROCATE — **re·tal·i·a·tion** \ri-ˌta-lē-'ā-shən, ˌrē-\ *n* — **re·tal·i·a·tive** \ri-'ta-lē-ˌā-tiv\ *adj* — **re·tal·ia·to·ry** \-'tal-yə-ˌtōr-ē, -'ta-lē-ə-, -ˌtȯr-\ *adj*

¹re·tard \ri-'tärd\ *vb* [ME, fr. MF or L; MF *retarder*, fr. L *retardare*, fr. *re-* + *tardus* slow] *vt* (15c) **1** : to slow up esp. by preventing or hindering advance or accomplishment : IMPEDE **2** : to delay academic progress by failure to promote ~ *vi* : to undergo retardation *syn* see DELAY — **re·tard·er** *n*

²re·tard *n* (1788) **1** \ri-'tärd\ : a holding back or slowing down : RETARDATION **2** \'rē-ˌtärd\ : a retarded person; *also* : a person held to resemble a retarded person in behavior — often taken to be offensive

re·tar·dant \ri-'tär-dᵊnt\ *adj* (1642) : serving or tending to retard ⟨a growth-*retardant* substance⟩ — **retardant** *n*

re·tar·date \-'tär-ˌdāt, -dət\ *n* (1915) : a mentally retarded person

re·tar·da·tion \ˌrē-ˌtär-'dā-shən, ri-\ *n* (15c) **1** : an act or instance of retarding **2** : the extent to which something is retarded **3** : a musical suspension; *specif* : one that resolves upward **4 a** : an abnormal slowness of thought or action; *also* : less than normal intellectual competence usu. characterized by an IQ of less than 70 **b** : slowness in development or progress

re·tard·ed \ri-'tär-dəd\ *adj* (1895) : slow or limited in intellectual or emotional development or academic progress

retch \'rech, *esp Brit* 'rēch\ *vb* [(assumed) ME *rechen* to spit, retch, fr. OE *hræcan* to spit, hawk; akin to ON *hrækja* to spit] *vi* (ca. 1798) : VOMIT 1 ~ *vi* : to make an effort to vomit; *also* : VOMIT — **retch** *n*

re·te \'rē-tē, 'rā-\ *n, pl* **re·tia** \'rē-tē-ə, 'rā-\ [NL, fr. L, net] (1541) **1** : a network esp. of blood vessels or nerves : PLEXUS **2** : an anatomical part resembling or including a network

re·tell \(ˌ)rē-'tel\ *vt* **-told** \-'tōld\; **-tell·ing** (1593) **1** : to tell again or in another form **2** : to count again

re·tell·ing *n* (1883) : a new version of a story ⟨a ~ of a Greek legend⟩

re·ten·tion \ri-'ten(t)-shən\ *n* [ME *retencioun*, fr. L *retention-*, *retentio*,

A RANDOMIZED COMPARISON OF CORONARY-STENT PLACEMENT AND BALLOON ANGIOPLASTY IN THE TREATMENT OF CORONARY ARTERY DISEASE

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Abstract *Background.* Coronary-stent placement is a new technique in which a balloon-expandable, stainless-steel, slotted tube is implanted at the site of a coronary stenosis. The purpose of this study was to compare the effects of stent placement and standard balloon angioplasty on angiographically detected restenosis and clinical outcomes.

Methods. We randomly assigned 410 patients with symptomatic coronary disease to elective placement of a Palmaz–Schatz stent or to standard balloon angioplasty. Coronary angiography was performed at base line, immediately after the procedure, and six months later.

Results. The patients who underwent stenting had a higher rate of procedural success than those who underwent standard balloon angioplasty (96.1 percent vs. 89.6 percent, P = 0.011), a larger immediate increase in the diameter of the lumen (1.72±0.46 vs. 1.23±0.48 mm, P<0.001), and a larger luminal diameter immediately after the procedure (2.49±0.43 vs. 1.99±0.47 mm, P<0.001). At six months, the patients with stented lesions continued to have a larger luminal diameter (1.74±0.60 vs. 1.56±0.65 mm, P = 0.007) and a lower rate of restenosis (31.6 percent vs. 42.1 percent, P = 0.046) than those treated with balloon angioplasty. There were no coronary events (death; myocardial infarction; coronary-artery bypass surgery; vessel closure, including stent thrombosis; or repeated angioplasty) in 80.5 percent of the patients in the stent group and 76.2 percent of those in the angioplasty group (P = 0.16). Revascularization of the original target lesion because of recurrent myocardial ischemia was performed less frequently in the stent group than in the angioplasty group (10.2 percent vs. 15.4 percent, P = 0.06).

Conclusions. In selected patients, placement of an intracoronary stent, as compared with balloon angioplasty, results in an improved rate of procedural success, a lower rate of angiographically detected restenosis, a similar rate of clinical events after six months, and a less frequent need for revascularization of the original coronary lesion. (N Engl J Med 1994;331:496-501.)

THE long-term benefit of coronary balloon angioplasty is limited by the possibility of restenosis of the treated segment, which occurs in approximately 30 to 50 percent of patients.[1-4] Restenosis can be caused by several factors, including elastic recoil of the dilated artery, platelet-mediated thrombus formation, proliferation of smooth-muscle cells, and vascular remodeling.[5] When restenosis develops, it is frequently associated with recurrent myocardial ischemia that necessitates additional revascularization procedures. New approaches to coronary intervention have therefore been developed with the aim of reducing the possibility of restenosis. Debulking coronary atheroma with lasers or atherectomy has not improved the problem of restenosis.[6-9] However, preliminary evidence suggests that stents may reduce the chance of restenosis by decreasing the elastic recoil of the vessel and sealing intimal flaps, thus providing a wider, smoother coronary lumen.[10,11] To test this hypothesis, we conducted a prospective, randomized trial to compare the rates of restenosis with coronary-stent placement and standard balloon angioplasty.

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*Additional participants in the Stent Restenosis Study (STRESS) trial are listed in the Appendix.

METHODS

Participating Centers and Investigators

The study centers and investigators were selected on the basis of their experience with implantation of Palmaz–Schatz coronary stents. The study protocol was approved by the institutional review board at each of the 20 centers participating in the trial.

Patient Selection

The study population consisted of patients with symptomatic ischemic heart disease and new lesions of the native coronary circulation. The specific angiographic criteria for enrollment included at least 70 percent stenosis, according to the estimate of the investigators; a lesion that was 15 mm or less in length and could be spanned by a single stent; and a vessel diameter of at least 3.0 mm. The criteria for exclusion were a myocardial infarction within the previous seven days; a contraindication to aspirin, dipyridamole, or warfarin sodium; and a left ventricular ejection fraction of 40 percent or less. The angiographic criteria for exclusion were evidence of coronary thrombus, the presence of multiple focal lesions or diffuse disease, serious disease in the left main coronary artery, ostial lesions, and severe vessel tortuosity.

Randomization

After the patients had been interviewed to determine their eligibility and had given their informed consent, they were randomly

assigned to either stent placement or balloon angioplasty. Randomization of the patients, stratified according to center with a block design, was carried out by means of sealed envelopes. The randomization sequence was developed so that an equal number of patients would be assigned to each treatment at each center.

Procedural Protocol

Stent Placement

The Palmaz–Schatz stent is composed of two rigid 7-mm slotted stainless-steel tubes connected by a 1-mm central bridging strut (Johnson and Johnson Interventional Systems, Warren, N.J.). The stent, which is 1.6 mm in diameter in the unexpanded state, is mounted on a balloon catheter and protected by an outer sheath during passage to the target site. When the sheath is withdrawn, inflation of the balloon catheter expands the stent. Technical details of the design and placement of the Palmaz–Schatz coronary stent have been described elsewhere.[12,13]

Patients assigned to stent placement received nonenteric aspirin (325 mg daily), dipyridamole (75 mg three times a day), and treatment with a calcium-channel antagonist, initiated at least 24 hours before the procedure. In addition, patients received intravenous low-molecular-weight dextran (dextran 40, given at a dose of 100 ml per hour for two hours before stenting and at a dose of 50 ml per hour during and after the procedure, for a total volume of 1 liter). During the procedure, patients received an initial bolus injection of heparin (10,000 to 15,000 units) supplemented as needed to maintain an activated clotting time of more than 300 seconds. The heparin infusion was discontinued at the termination of the procedure and reinstituted four to six hours after hemostasis of the site of vascular access had been achieved. Warfarin sodium was begun on the day of the procedure. Heparin and warfarin sodium were both administered for at least 72 hours or until a prothrombin time of 16 to 18 seconds had been achieved (international normalized ratio, 2.0 to 3.5). After patients were discharged from the hospital, dipyridamole and warfarin sodium were continued for one month, and aspirin was continued indefinitely.

Angioplasty Protocol

Angioplasty was performed with the use of conventional techniques. Aspirin was prescribed, but warfarin sodium was not administered. Investigators attempted to achieve an optimal result with balloon angioplasty, which was defined as residual stenosis of less than 30 percent of the luminal diameter, according to a visual estimate. A crossover to stent placement was permitted as a "bail-out" procedure in the case of abrupt or threatened closure, defined as a dissection of the artery with compromised antegrade blood flow (Thrombolysis in Myocardial Infarction [TIMI] grade, <3) or persistent stenosis of over 50 percent of the luminal diameter in association with evidence of myocardial ischemia (chest pain, electrocardiographic changes, or both).

Follow-up

Patients were required to have clinical follow-up studies after one, three, and six months. Coronary angiography was required at six months in all the patients except those who had died or undergone coronary-artery bypass surgery or repeated angioplasty for abrupt closure during the first 14 days after the initial revascularization. Angiography performed before four months was allowed on the basis of clinical indications. However, if restenosis was not found, a subsequent angiogram was obtained after four months.

Angiographic Analysis

Angiography was performed in two orthogonal views. Intracoronary nitroglycerin (200 mg) was injected before all angiographic assessments. Angiograms were analyzed at the Core Angiographic Laboratory at Jefferson Medical College. Quantitative analysis was performed with the use of a validated edge-detection algorithm.[14] Vessel edges were determined with the computerized algorithm, and luminal diameters were measured with the dye-filled catheter as a reference. The diameters of the normal segments proximal and distal to the treated area were averaged to determine the reference diameter. The minimal luminal diameter, reference diameter, and percentage of stenosis were calculated as the mean values from two orthogonal projections. The percentage of elastic recoil was defined as the largest inflated-balloon diameter minus the postprocedural minimal luminal diameter divided by the inflated-balloon diameter. In addition, coronary lesions were assessed for eccentricity, calcification, thrombus, plaque ulceration, tortuosity, and postprocedural dissection. Definitions used for this morphologic analysis and prior validation studies of the quantitative angiographic analysis have been described elsewhere.[11,13,15]

End Points

The primary end point of the trial was angiographic evidence of restenosis, defined as at least 50 percent stenosis on the follow-up angiogram. Secondary angiographic end points included angiographic evidence of procedural success and the absolute minimal luminal diameter after the procedure and at follow-up. Angiographic evidence of procedural success was defined as a reduction in stenosis to 50 percent or less by quantitative analysis.

Clinical evidence of procedural success was defined as angiographic evidence of success without a major complication (death, myocardial infarction, or coronary-artery bypass surgery) during the index hospitalization. The secondary clinical end point was a composite end point, defined as whichever of the following occurred first: death, myocardial infarction, coronary bypass surgery, or the need for repeated angioplasty within the first 6 months (±60 days) after the initial revascularization. Myocardial infarction was documented by the presence of new Q waves of at least 0.04 second's duration or a creatine kinase level or MB fraction at least twice the upper limit of normal. Clinical events were classified as early (occurring from day 0 to day 14) or late (occurring after 14 days). Revascularization of the target lesion was defined as angioplasty or bypass surgery performed because of restenosis of the target lesion in association with recurrent angina, objective evidence of myocardial ischemia, or both. Other events included abrupt vessel closure (after the patient had left the catheterization laboratory) and hemorrhagic complications, defined as a cerebrovascular accident, bleeding requiring transfusion, or the need for vascular surgery.

Clinical and angiographic data were forwarded to the Data Coordinating Center at the University of Pittsburgh for statistical analyses. Adverse events were audited and reviewed by members of the Steering Committee. The primary analysis of angiographic and procedural outcomes was based on the intention-to-treat principle. We also performed a secondary analysis of the rate of restenosis according to the treatment received.

For the analysis of continuous data, two-tailed t-tests were used to assess differences between the two treatment groups. The results are expressed as means ±SD. Categorical data, which are presented as rates, were compared by chi-square test, except for the composite clinical end point and revascularization of the target lesion, which were analyzed by means of Kaplan–Meier survival curves, with differences between the two treatment groups compared by Wilcoxon test.[16] Multiple linear regression was used to assess the relation between the luminal diameter at follow-up and multiple clinical and angiographic variables, including age, sex, location of the lesion, vessel diameter, and postprocedural luminal diameter.

Results

Between January 1991 and February 1993, 410 patients were enrolled in the study; 207 patients were randomly assigned to stent placement, and 203 to angioplasty. After randomization, three patients (two in the stent group and one in the angioplasty group) were excluded because they did not meet all the enrollment criteria. Thus, the final study group comprised 407 patients. Their base-line clinical and angiographic characteristics are shown in Table 1. More

men were assigned to the stent group than to the angioplasty group, and the patients in the stent group had lesions that were slightly longer, with a higher incidence of eccentricity, but the two groups were well matched with respect to other clinical characteristics.

Procedural and Early Clinical Outcome

Stents were placed in 197 of the 205 patients (96.1 percent) randomly assigned to this therapy. One patient, in whom stent placement failed because of an inability to cross the lesion with a guide wire, was treated medically. Seven patients were switched to angioplasty: three because of an inability to place the stent and four because of lesion characteristics deemed unfavorable for stent placement at the time of the procedure. In the angioplasty group, six patients required emergency coronary-artery bypass surgery. In addition, 15 patients were switched to alternative therapies: 14 (6.9 percent) to emergency stent placement as a bailout procedure (1 of the 14 subsequently required emergency bypass surgery) and 1 to directional atherectomy.

Table 1. Base-Line Clinical and Angiographic Characteristics of Patients Assigned to Stent Placement or Angioplasty.*

Characteristic	Stent Group (N = 205)	Angioplasty Group (N = 202)
Male — % of patients	83	73†
Age — yr	60±10	60±10
Diabetes — % of patients	15	16
Hypertension — % of patients	43	45
Hyperlipidemia — % of patients	44	48
Current smoker — % of patients	21	24
History of myocardial infarction — % of patients	37	36
Recent myocardial infarction (within previous 6 wk) — % of patients	18	15
Unstable angina — % of patients	47	48
Pain at rest	33	39
Pain with electrocardiographic changes	23	26
Postinfarction angina	7	6
No. of diseased vessels — % of patients		
1	64	68
2	27	21
3	9	11
Ejection fraction — %	61±12	61±11
Target vessel — % of patients		
Left anterior descending	47	48
Left circumflex	16	13
Right coronary artery	37	39
Calcification — % of patients	17	15
Thrombus — % of patients		
Definite	2	1
Possible	15	9
Eccentricity — % of patients	66	54‡
Lesion angulation >45° — % of patients	13	18
Lesion length — mm	9.6±3.0	8.7±2.7§
Stenosis — % of luminal diameter	75±9	75±8

*Plus–minus values are means ±SD.
†P≤0.05.
‡P = 0.02.
§P<0.001.

Table 2. Procedural Outcomes and Clinical Events.

Variable	Stent Group (N = 205)	Angioplasty Group (N = 202)	P Value
	% of patients		
Procedural outcome			
Angiographic success			
Reading at study center	99.5	96.5	0.04
Quantitative analysis	99.5	92.6	<0.001
Clinical success	96.1	89.6	0.011
Early events (0–14 days)			
Death	0	1.5	0.12
Myocardial infarction/Q wave	5.4/2.9	5.0/3.0	0.85/1.0
Coronary bypass surgery	2.4	4.0	0.38
Abrupt closure*	3.4	1.5	0.34
Repeated angioplasty	2.0	1.0	0.69
Any event	5.9	7.9	0.41
Late events (15–240 days)			
Death	1.5	0	0.25
Myocardial infarction/Q wave	1.5/1.0	2.0/0.5	0.72/1.0
Coronary bypass surgery	2.4	4.5	0.26
Repeated angioplasty	9.8	11.4	0.59
Target-vessel revascularization	10.2	15.4	0.06
Any event	15.1	15.8	0.84
All events (0–240 days)			
Death	1.5	1.5	0.99
Myocardial infarction/Q wave	6.3/3.4	6.9/3.5	0.81/0.98
Coronary bypass surgery	4.9	8.4	0.15
Repeated angioplasty	11.2	12.4	0.72
Any event	19.5	23.8	0.16
Bleeding and vascular complications			
Cerebrovascular accident	1.0	0.5	1.0
Surgical vascular repair	3.9	2.0	0.25
Bleeding requiring transfusion	4.9	2.5	0.11
Any event	7.3	4.0	0.14

*After the patient left the catheterization laboratory.

Procedural and early clinical outcomes are shown in Table 2. According to the quantitative analysis, there was angiographic evidence of procedural success in 204 of the 205 patients (99.5 percent) randomly assigned to undergo stent placement and in 187 of the 202 patients (92.6 percent) randomly assigned to undergo angioplasty (P<0.001). The clinical success rates were 96.1 percent and 89.6 percent, respectively (P = 0.011).

Abrupt vessel closure occurred in 10 patients after they had left the catheterization laboratory: 7 in the stent group and 3 in the angioplasty group (3.4 and 1.5 percent, respectively; P = 0.34). In the three patients in the angioplasty group, the closure occurred after the stent had been placed as a bailout measure. Abrupt closure occurred an average of 6 days (range, 2 to 14) after the procedure, and in 6 of the 10 patients, it occurred after hospital discharge. All the patients with abrupt closures had major cardiac events (two died and eight had nonfatal myocardial infarctions). The proportions of patients with any major cardiac event (death, myocardial infarction, coronary bypass surgery, or repeated angioplasty within 14 days after the procedure) were 5.9 percent in the stent group and 7.9 percent in the angioplasty group

(Table 2). Bleeding and vascular complications occurred more commonly in the stent group than in the angioplasty group (7.3 percent vs. 4.0 percent, P = 0.14). The hospital stay after the procedure was longer in the stent group (5.8 days vs. 2.8 days, P<0.001).

Angiographic Results

Angiography was repeated at six months in 336 of the 383 patients (88 percent) eligible for follow-up. Angiography was not repeated in 28 patients in the stent group because of refusal (15 patients) or ineligibility due to stent thrombosis (7), death (3), early coronary bypass surgery (2), or inability to perform the study procedures (1). In the angioplasty group, 43 patients did not have follow-up angiography because of refusal (32) or ineligibility due to early coronary bypass surgery (7), abrupt vessel closure (3), or death (1). The rate of restenosis was 31.6 percent (56 of 177 patients) in the stent group and 42.1 percent (67 of 159) in the angioplasty group (P = 0.046). The rates of restenosis among the patients who received their assigned therapy were 30.0 percent in the stent group and 43.0 percent in the angioplasty group (P = 0.016).

The luminal dimensions at base line, immediately after the procedure, and at follow-up are shown in Table 3. At base line, there was no difference in the reference diameter or the severity of stenosis between the two groups. After the procedure, a larger immediate gain in the luminal diameter was achieved in the patients who underwent stent placement than in those who underwent angioplasty, resulting in a larger mean (±SD) diameter in the stent group (2.49±0.43 vs. 1.99±0.47 mm, P<0.001). At follow-up, the stent group had a larger mean reduction in the luminal diameter (0.74±0.58 vs. 0.38±0.66 mm, P<0.001) but a larger net gain, resulting in a larger luminal diameter at follow-up (1.74±0.60 vs. 1.56±0.65 mm, P = 0.007). These data are shown in Figure 1. A stepwise linear regression analysis showed that the luminal diameter immediately after the procedure was the most important predictor of the luminal diameter at six months (b = 0.41, P<0.001), irrespective of the procedure used. Additional important determinants included a larger reference diameter (b = 0.31, P<0.001) and location of the lesion in a vessel other than the left anterior descending coronary artery (b = 0.14, P = 0.029).

Late Clinical Follow-up

Data on late cardiac events and all events are shown in Table 2. Clinical follow-up data were available for 406 of the 407 patients. Although the numbers of patients who died or had myocardial infarctions were comparable in the two groups, fewer patients in the stent group underwent revascularization of the target lesion (10.2 percent vs. 15.4 percent, P = 0.06) (Fig. 2). Event-free survival was 80.5 percent in the stent group, as compared with 76.2 percent in the angioplasty group (P = 0.16) (Fig. 3). Among the patients eligible for follow-up, a larger proportion of those in the stent group remained free of angina (78.9 percent vs. 71.1 percent, P = 0.076).

Table 3. Angiographic Results in the Stent and Angioplasty Groups.*

Variable	Stent Group (N = 205)	Angioplasty Group (N = 202)	P Value
Before the procedure			
Reference vessel (mm)	3.03±0.42	2.99±0.50	0.30
Minimal luminal diameter (mm)	0.77±0.27	0.75±0.25	0.48
Stenosis (% of luminal diameter)	75±9	75±8	0.81
After the procedure			
Reference vessel (mm)	3.05±0.40	2.99±0.46	0.15
Minimal luminal diameter (mm)	2.49±0.43	1.99±0.47	<0.001
Stenosis (% of luminal diameter)	19±11	35±14	<0.001
Elastic recoil (%)	15±11	24±15	<0.001
Dissection (% of patients)	7	25	<0.001
At follow-up			
Reference vessel (mm)	3.00±0.41	2.98±0.49	0.74
Minimal luminal diameter (mm)	1.74±0.60	1.56±0.65	0.007
Stenosis (% of luminal diameter)	42±18	49±19	0.001
Restenosis (% of patients)	31.6	42.1	0.046
Change in minimal luminal diameter			
Immediate gain (mm)	1.72±0.46	1.23±0.48	<0.001
Late loss (mm)	0.74±0.58	0.38±0.66	<0.001
Net gain (mm)	0.98±0.62	0.80±0.63	0.01

*Plus–minus values are means ±SD. Immediate gain refers to the minimal luminal diameter immediately after the procedure minus the diameter before the procedure. Late loss refers to the minimal luminal diameter immediately after the procedure minus the diameter at follow-up. Net gain refers to the minimal luminal diameter at follow-up minus the diameter before the procedure.

Discussion

In this trial, we compared stent placement with balloon angioplasty for the treatment of new focal coronary stenoses in larger vessels; we found a reduc-

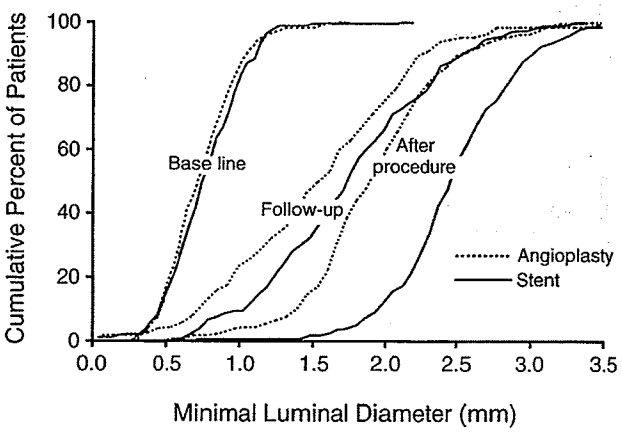

Figure 1. Minimal Diameter of the Lumen at Base Line, Immediately after Stent Placement or Angioplasty, and at Follow-up.

There was no difference in base-line values between the stent and angioplasty groups. Immediately after the procedure, the patients in the stent group had a larger minimal luminal diameter than those in the angioplasty group. Six months later, both groups had reduced values, and a significant difference in diameter persisted between the two groups.

tion in the rate of angiographic restenosis at six months with the stenting procedure. This reduction was associated with a reduction in the need for repeat revascularization due to ischemia-associated restenosis.

Our findings contrast with those of previous investigations that examined the efficacy of pharmacologic agents in preventing restenosis.[17-24] Of the newer interventional procedures, only directional atherectomy has been subjected to careful prospective, randomized studies to assess its efficacy in reducing restenosis, as compared with the efficacy of angioplasty.[7,8] Those studies showed either no benefit of atherectomy or a minimal reduction in restenosis with more frequent major complications.

Like the Coronary Angioplasty versus Excisional Atherectomy Trial (CAVEAT),[7] our study shows that the most important determinant of the luminal diameter at six months was the luminal diameter achieved immediately after the procedure. It seems plausible that the reduction in restenosis in our stent group was due to the significantly larger luminal diameter obtained immediately after placement of the stent, as compared with the luminal diameter immediately after angioplasty. The residual stenosis in the stent group (19 percent) was roughly half that in the angioplasty group (35 percent) and 10 percentage points less than the residual stenosis in patients undergoing directional atherectomy.[7] Although the larger immediate gain in luminal diameter was offset by a larger subsequent loss, the net gain remained larger in the patients in the stent group (Fig. 1). Multivariate analysis showed that the luminal diameter immediately after the procedure was the most powerful predictor of the luminal diameter at follow-up, regardless of whether stenting or balloon angioplasty achieved this result. Therefore, it was not the specific technique used, but rather its efficacy in achieving a larger luminal diameter that was the determining factor, an idea that has been suggested previously.[25] In addition, stenting resulted in a larger diameter with less risk of intimal disruption and elastic recoil, thereby acting as an effective intravascular scaffold. The ability of the stent to serve as a scaffold was further demonstrated in the 14 patients in the angioplasty group (6.9 percent) who were switched to stent placement for treatment of imminent or actual closure after balloon angioplasty had failed. At the inception of this trial, stent placement as a bailout measure, which at the time was not available as a routine procedure, was considered equivalent to emergency coronary-artery bypass surgery. Thirteen of the 14 patients who underwent stent placement as a bailout measure had balloon-induced dissections or luminal compromise associated with chest pain or electrocardiographic changes, suggesting that these patients would have had serious clinical events if stent placement had not been available. Therefore, the availability of stent placement probably decreased the rate of clinical events in the angioplasty group. This study thus represents a comparison of two treatment strategies: elective stent placement and elective balloon angioplasty with stent placement available as a bailout measure.

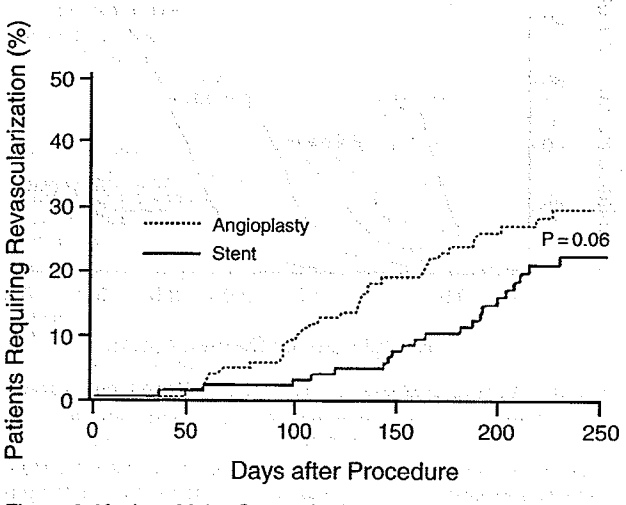

Figure 2. Kaplan–Meier Curves for Revascularization of the Target Lesion.

Fewer patients in the stent group than in the angioplasty group required revascularization of the target lesion because of ischemia.

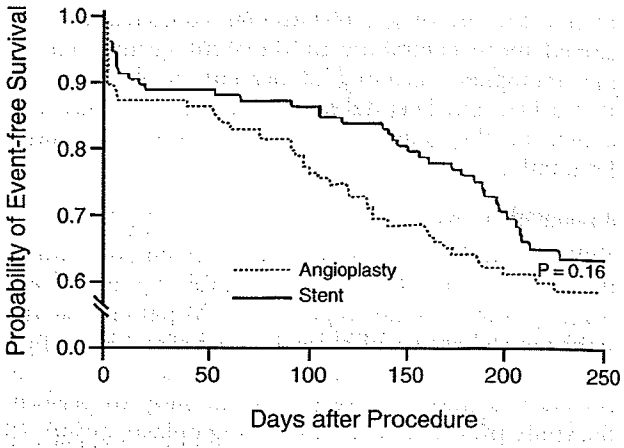

Figure 3. Kaplan–Meier Survival Curves for Major Cardiac Events (Death, Myocardial Infarction, Coronary-Artery Bypass Surgery, and Repeated Angioplasty).

Several limitations of stent placement need to be emphasized. Stent thrombosis occurred in 3.4 percent of the patients who underwent stent placement as an elective procedure and in 21.4 percent of those in whom stent placement was used as a bailout technique. These thrombotic events occurred 2 to 14 days after placement of the stent, with six instances of thrombosis after discharge, and invariably resulted in major clinical complications. Furthermore, the intense anticoagulation and antiplatelet regimen associated with stent placement resulted in nearly twice the number of hemorrhagic and peripheral vascular complications associated with angioplasty, as well as a prolonged hospital stay.

Although the frequency with which follow-up angiography was performed was relatively high in both

groups, there was a higher rate of angiographic follow-up in the stent group (92 percent vs. 83 percent, $P = 0.008$). This difference, which may bias the rate of restenosis in favor of stent placement, is a limitation of the study.

In conclusion, elective stent placement, as compared with angioplasty, has a higher clinical success rate and reduces the incidence of restenosis and the need for subsequent revascularization of the treated lesion. The reduction in restenosis is not associated with an increase in major cardiac events, despite the limitations imposed by stent thrombosis and hemorrhagic complications. The use of antithrombotic stent coatings, improved techniques to optimize expansion of the stent during implantation, and compression and closure devices at the site of arteriotomy may address these limitations. If they are effectively overcome, implantation of the Palmaz–Schatz stent may become the preferred treatment in selected patients with new lesions in large coronary arteries.

Appendix

The following institutions and investigators participated in the STRESS trial: Arizona Heart Institute, Phoenix (E. Davis, W. Catran, and K. Waters); Beth Israel Hospital, Boston (D.J. Diver, J. Carrozza, and C. Senerchia); Centro Cuore Columbus, Milan, Italy (Y. Almagor and M. Bernati); Cleveland Clinic Foundation, Cleveland (P. Whitlow); Florida Heart Hospital, Orlando (C. Curry, C.B. Saenz, W.H. Willis, Jr., R.J. Ivanhoe, and N. Granger); Hospital of the University of Pennsylvania, Philadelphia (H. Herman, D. Kolansky, W. Laskey, and D. DiAngelo); Johns Hopkins Hospital, Baltimore (V. Coombs); Lenox Hill Hospital, New York (E.M. Kreps, J. Strain, N. Cohen, J. Higgins, and C. Undemir); Scripps Clinic and Research Foundation, San Diego, Calif. (N. Morris and M. Dowling); St. Luke's Hospital, Houston (M. Harlan and B. Lambert); Thomas Jefferson University Hospital, Philadelphia (A. Zalewski, P. Walinsky, and D. Porter); Toronto General Hospital, Toronto (L. Lazzam, C. Lazzam, and P. Slaughter); University of Texas at San Antonio, San Antonio (J.P. Hennecken, S. Kiesz, and A. Briscoe); Vancouver General Hospital, Vancouver, B.C. (C.E. Buller and A. McCarthy); Victoria General Hospital, Halifax, N.S. (B. O'Neil, C.J. Foster, C.M. Peck, K.A. Foshay, and N.L. Fitzgerald); Victoria Hospital, London, Ont. (N. Murray-Parson and L. Marziali); Washington Cardiology Center, Washington, D.C. (K. Donovan); Yale University, New Haven, Conn. (H.S. Cabin and R.E. Rosen); *Data Coordinating Center:* Department of Epidemiology, University of Pittsburgh, Pittsburgh (K. Detre, V. Niedermeyer, L. Kennard, and L. Vetri); *Core Angiographic Laboratory:* Thomas Jefferson University Hospital, Philadelphia (R. Rake, S. Gebhardt, D.L. Fischman, M.P. Savage, and S. Goldberg); *Steering Committee:* D.S. Baim, S. Goldberg, M.B. Leon, I. Penn, and R.A. Schatz.

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A COMPARISON OF BALLOON-EXPANDABLE–STENT IMPLANTATION WITH BALLOON ANGIOPLASTY IN PATIENTS WITH CORONARY ARTERY DISEASE

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Abstract *Background.* Balloon-expandable coronary-artery stents were developed to prevent coronary restenosis after coronary angioplasty. These devices hold coronary vessels open at sites that have been dilated. However, it is unknown whether stenting improves long-term angiographic and clinical outcomes as compared with standard balloon angioplasty.

Methods. A total of 520 patients with stable angina and a single coronary-artery lesion were randomly assigned to either stent implantation (262 patients) or standard balloon angioplasty (258 patients). The primary clinical end points were death, the occurrence of a cerebrovascular accident, myocardial infarction, the need for coronary-artery bypass surgery, or a second percutaneous intervention involving the previously treated lesion, either at the time of the initial procedure or during the subsequent seven months. The primary angiographic end point was the minimal luminal diameter at follow-up, as determined by quantitative coronary angiography.

Results. After exclusions, 52 patients in the stent group (20 percent) and 76 patients in the angioplasty group (30 percent) reached a primary clinical end point (relative risk, 0.68; 95 percent confidence interval, 0.50 to 0.92; P = 0.02). The difference in clinical-event rates was explained mainly by a reduced need for a second coronary angioplasty in the stent group (relative risk, 0.58; 95 percent confidence interval, 0.40 to 0.85; P = 0.005). The mean (±SD) minimal luminal diameters immediately after the procedure were 2.48±0.39 mm in the stent group and 2.05±0.33 mm in the angioplasty group; at follow-up, the diameters were 1.82±0.64 mm in the stent group and 1.73±0.55 mm in the angioplasty group (P = 0.09), which correspond to rates of restenosis (diameter of stenosis, ≥50 percent) of 22 and 32 percent, respectively (P = 0.02). Peripheral vascular complications necessitating surgery, blood transfusion, or both were more frequent after stenting than after balloon angioplasty (13.5 vs. 3.1 percent, P<0.001). The mean hospital stay was significantly longer in the stent group than in the angioplasty group (8.5 vs. 3.1 days, P<0.001).

Conclusions. Over seven months of follow-up, the clinical and angiographic outcomes were better in patients who received a stent than in those who received standard coronary angioplasty. However, this benefit was achieved at the cost of a significantly higher risk of vascular complications at the access site and a longer hospital stay. (N Engl J Med 1994;331:489-95.)

IMPLANTATION of an intracoronary stent in conjunction with balloon angioplasty is not only highly effective in treating acute vessel closure due to balloon-induced dissection, but it may also reduce the rate of restenosis.[1-4] Unfortunately, all stents currently available are metallic and thus thrombogenic, a problem that necessitates anticoagulation therapy.[5,6] This therapy exposes the patient to an increased risk of major bleeding and vascular complications, which may prolong the hospital stay.[7] Despite these drawbacks and although the superiority of stent implantation over standard balloon angioplasty has not yet been proved, stenting has been used increasingly. Therefore, we conducted a multicenter, randomized study comparing stent implantation and balloon angioplasty with respect to their safety and efficacy

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*The remaining investigators in the Benestent Study Group are listed in the Appendix.

in patients with stable angina pectoris and a single new lesion in a coronary artery.

Methods

Selection of Patients

Patients scheduled to undergo coronary angioplasty because of stable angina due to a single new lesion in a coronary artery were eligible for the study if they had no contraindication to anticoagulant or antiplatelet therapy and if they were also suitable candidates for coronary bypass surgery. The target lesion needed to be less than 15 mm long and to be located in a vessel more than 3 mm in diameter that supplied normally functioning myocardium. Patients with an ostial lesion, a lesion at a bifurcation, or a lesion in a previously grafted vessel were excluded from the study, as were patients in whom an intracoronary thrombus was suspected.

The study was carried out according to the principles of the Declaration of Helsinki. Oral or written informed consent according to local practice was obtained for every patient.

Randomization

Patients were randomly assigned by telephone from a central office to either implantation of a Palmaz–Schatz stent or balloon angioplasty. To ensure an equal distribution of treatments in each center, we developed the randomization sequence on a site basis in blocks of six treatment assignments.

Balloon Angioplasty and Stent Implantation

Balloon angioplasty and stent implantation were performed according to standard clinical practice by the femoral approach. The stent was deployed by inflating a balloon over which the collapsed stent was fitted. Inflation of the balloon expanded the stent. After the implantation of the stent, the stented area was often dilated further by standard balloon angioplasty. All patients received 250 to 500 mg of aspirin daily and 75 mg of dipyridamole three times a day; this treatment was started the day before the procedure and was continued for six months. During the procedure, patients receiving a stent were treated with a continuous infusion of dextran (1000 ml) and a bolus dose of 10,000 U of heparin, repeated if necessary, followed by a combination of heparin and oral anticoagulation therapy (with warfarin) after the removal of the sheath and titrated by measuring the prothrombin time and either the activated partial-thromboplastin time or the activated clotting time. The dose of heparin was decreased progressively after the prothrombin time had been in the therapeutic range (international normalized ratio, 2.5 to 3.5) for at least 36 hours. Warfarin therapy was continued for three months. The patients who underwent balloon angioplasty received only 10,000 U of heparin during that procedure, followed by an additional bolus dose or a continuous infusion if deemed necessary. In addition, both treatment groups received calcium antagonists until discharge from the hospital.

Clinical and Angiographic Follow-up

Patients were seen in the outpatient clinic after one, three, and six months for an interview, physical examination, and electrocardiogram. Exercise testing was performed before the second cardiac catheterization and coronary angiography at six months. If a revascularization procedure involving the treated segment had been performed before the six-month angiography, the most recent angiogram obtained before this intervention, if available, was used as the follow-up angiogram, regardless of the timing of the second intervention. If the time to follow-up angiography was less than three months and no second intervention was performed, the patient was asked to undergo angiography again at six months. In the absence of a second angiogram at six months, the angiogram obtained most recently within the previous three months was used, if available, provided that no end point had occurred.

Three angiograms were obtained for each patient — one just before the intervention, one immediately after, and one at follow-up. All the angiograms were analyzed by the Cardiovascular Angiography Analysis System and sent to the core laboratory (Cardialysis, Rotterdam, the Netherlands). To standardize the method of data acquisition and to ensure the exact reproducibility of the angiograms performed after the intervention and at follow-up, measurements were made as described earlier.[8]

End Points

The primary clinical end points were whichever of the following occurred first: death, a cerebrovascular accident, myocardial infarction, bypass surgery, or a second percutaneous intervention involving the previously treated lesion between the time of the initial procedure and the angiography performed at 6 months (±4 weeks) (or at 7 months if no angiography was performed at 6 months). The indication for a second intervention or for bypass surgery had to be substantiated by symptoms or by electrocardiographic or scintigraphic evidence of myocardial ischemia at rest or during exercise. All events were reviewed by the critical-event committee, which was unaware of the treatment assignments.

Death was defined to include all deaths, regardless of cause. Cerebrovascular accidents occurring in patients receiving anticoagulant therapy were considered to be intracranial hemorrhages unless unequivocally demonstrated otherwise. Myocardial infarction was diagnosed if there were new pathologic Q waves according to the Minnesota Code[9] or if there was an increase in serum creatine kinase to more than twice the normal value, together with a pathologic increase in myocardial isoenzymes. Bypass surgery was defined to include emergency or elective bypass surgery involving the previously treated segment. Emergency bypass surgery was defined as involving an immediate transfer from the angioplasty suite to the operating room during the initial phase of treatment. "Bailout" stent implantation was defined as the placement of a stent in the event of Thrombolysis in Myocardial Infarction (TIMI) grade 0 or 1 flow after angioplasty or in the case of worsening of the base-line TIMI flow by one grade.[10] In all instances, prolonged balloon angioplasty had to be attempted before bailout stenting was considered. By design, stent implantation as a bailout procedure was considered equivalent to emergency bypass surgery but was removed retroactively from the analysis of primary end points, since it is currently perceived as an integral part of an angioplasty strategy. Only the untoward clinical events associated with such stenting were counted as end points. Second interventions were those involving a previously treated lesion that followed the initial procedure, which was considered complete when the guiding catheter was removed from the arterial sheath. Revascularization (surgical or percutaneous) involving other coronary arteries did not constitute an end point.

The primary angiographic end point was the minimal luminal diameter at follow-up. For each treated segment, this value was calculated from the mean values obtained in multiple matched projections.

Secondary end points included (1) the angiographic success rate, defined as the rate of achievement of less than 50 percent stenosis on visual assessment; (2) the procedural success rate, defined as the rate of achievement of less than 50 percent stenosis on quantitative assessment, without the occurrence of clinical events during the hospital stay; (3) the functional class according to the classification of the Canadian Cardiovascular Society at six months or at the time of intercurrent angiography and second intervention; (4) the results of exercise testing at six months or earlier, if clinically indicated; (5) the rate of restenosis (stenosis ≥50 percent at follow-up) at six months.

Power Calculations and Statistical Analysis

At the outset of the study, the size of the required sample (428 patients) was based on an assumed rate of clinical events of 30 percent in the angioplasty group and a reduction of that rate by 40 percent in the stent group (by a two-sided test with an alpha error of 0.05 and a power of 0.80). To compensate for unsuccessful interventions and losses to follow-up, the sample was enlarged by 10 percent (to 470 patients). In addition, to adjust for a loss of power due to a planned interim analysis, the sample was increased by another 10 percent, reaching a final size of 520 patients.[11]

The main clinical analysis consisted of a single comparison be-

tween the two study groups with respect to the primary clinical end point, regardless of its time of occurrence; this analysis involved all randomized patients with the exceptions of three patients found after randomization not to be eligible and of one patient who withdrew informed consent for further treatment and follow-up according to the intention-to-treat principle. The clinical events were ranked according to the highest category of severity on the following scale: death, cerebrovascular accident, myocardial infarction, emergency bypass surgery, elective bypass surgery, and repeat percutaneous intervention.

The main angiographic analysis consisted of a single comparison between the two study groups with respect to minimal luminal diameter and was performed according to the intention-to-treat principle.

Continuous variables are expressed as means ±SD and were compared by the unpaired Student's t-test. The chi-square test with Yates' correction was used to compare proportions. Discrete variables are expressed as counts and percentages and are compared in terms of relative risks (for stenting as compared with angioplasty), with 95 percent confidence intervals calculated by the formula of Greenland and Robins.[12] All statistical tests were two-tailed.

RESULTS

Characteristics of the Patients

Between June 1991 and March 1993, 520 patients were randomly assigned to stent implantation (262 patients) or balloon angioplasty (258 patients) at 28 participating centers. Of these 520 patients, 4 were excluded from further analysis, 3 in the stent group and 1 in the angioplasty group. One patient withdrew his informed consent and left the hospital without receiving treatment, two other patients did not undergo coronary revascularization because their lesions proved to be unimportant during on-line quantitative coronary angiography at the time of the intended intervention, and one patient participated in another study with an investigational drug. There were no differences in base-line characteristics between the two study groups (Tables 1 and 2).

Table 1. Base-Line Clinical Characteristics of the 516 Patients Included in the Intention-to-Treat Analysis.*

CHARACTERISTIC	ANGIOPLASTY (N = 257)	STENT (N = 259)
Age (yr)	58±10	57±9
Weight (kg)	79±13	78±11
Height (cm)	171±9	171±8
	no. (%)	*no. (%)*
Male sex	212 (82)	207 (80)
Ever smoked	124 (48)	119 (46)
Current smoker	60 (23)	62 (24)
Diabetes mellitus	16 (6)	17 (7)
Previous conditions		
Myocardial infarction	48 (19)	52 (20)
Coronary-artery bypass grafting	5 (2)	0
Angioplasty	8 (3)	5 (2)
Hypertension	89 (35)	80 (31)
Hypercholesterolemia	95 (37)	89 (34)
Stroke	6 (2)	6 (2)
Peripheral vascular disease	8 (3)	10 (4)
Exertional angina (CCS class)†		
I	9 (4)	9 (3)
II	75 (29)	82 (32)
III	130 (51)	125 (48)
IV	20 (8)	16 (6)
None	23 (9)	27 (10)
Mixed	89 (35)	89 (34)

*Plus–minus values are means ±SD.

†According to the classification system of the Canadian Cardiovascular Society (CCS).

In-Hospital Clinical Outcomes

Of the remaining 259 patients randomly assigned to receive stents, 14 (5.4 percent) did not receive a stent but were treated successfully with balloon angioplasty. The reasons for this crossover were the withdrawal of informed consent in five, the physician's preference because of the patient's unfavorable anatomy (e.g., small vessel size) or angiographic evidence of thrombus in three, and failure to cross the lesion with the stent in six. In addition, stent implantation was unsuccessful in 10 patients: 6 because the lesion was not dilated beforehand and 4 because the stent could not be deployed. Of these 10 patients, 8 underwent bypass surgery that was urgent in 3 and elective in 5. The remaining two patients, who unexpectedly had totally occluded coronary arteries that could not be recanalized, were treated medically.

Of the 257 remaining patients randomly assigned to balloon angioplasty, 13 (5.1 percent) received stents for the following reasons: acute vessel closure in 1, flow-limiting dissection in 11, and a suboptimal angiographic result in 1. Of these 13 patients, 2 were referred for urgent bypass surgery and 1 had a non–Q-wave myocardial infarction. In addition, three other patients who had complicated balloon angioplasty and in whom no bailout stent implantation was attempted underwent urgent bypass surgery. Therefore, the angiographic success rate was 96.9 percent in the stent group and 98.1 percent in the angioplasty group, whereas the procedural success rates were 92.7 and 91.1 percent, respectively.

The ranking and the total number of clinical events occurring in the hospital are shown in Table 3. The composite rate for all in-hospital events was similar in both groups (16 events or 6.2 percent in the angioplasty group vs. 18 events or 6.9 percent in the stent group; relative risk, 1.12; 95 percent confidence interval, 0.58 to 2.14). There were no in-hospital deaths in either group; one patient treated with balloon angioplasty had an intracranial hemorrhage. There was no difference between groups in the incidence of Q-wave and non–Q-wave infarction (3.1 percent in the angioplasty group vs. 3.4 percent in the stent group; relative risk, 1.12; 95 percent confidence interval, 0.44 to 2.85) or in the need for urgent or elective cardiac surgery or second angioplasty during the hospital stay (2.7 percent in the angioplasty group vs. 3.5 percent in the stent group; relative risk, 1.28; 95 percent confidence interval, 0.48 to 3.37).

Angiographically documented stent thrombosis during the hospital stay occurred in 3.5 percent of patients, an incidence similar to that of subacute vessel closure after balloon angioplasty (2.7 percent). It is noteworthy that no stent thrombosis occurred in the 13 patients treated with a bailout stent. However, the incidence of bleeding and vascular complications was

significantly higher after stent implantation than after balloon angioplasty (13.5 vs. 3.1 percent; relative risk, 4.34; 95 percent confidence interval, 2.05 to 9.18; P<0.001).

The mean hospital stay was 8.5 days in the stent group and 3.1 days in the angioplasty group (P<0.001).

Clinical Outcomes at Seven Months

The numbers of various types of clinical events at seven months among all 516 patients are shown in Table 3. A primary clinical end point was reached by 76 of the 257 patients randomly assigned to balloon angioplasty (30 percent), as compared with 52 of the 259 patients randomly assigned to stent implantation (20 percent) (relative risk, 0.68; 95 percent confidence interval, 0.50 to 0.92; P = 0.02). This difference in long-term clinical outcome is shown in the cumulative distribution curves for the primary clinical end point in both treatment groups (Fig. 1D). The favorable long-term outcome in the stent group was also partly reflected in the difference between the two groups in functional class at the time of the second angiography (Table 4). The most striking difference in clinical outcomes was the significantly reduced need for an elective second revascularization by means of percutaneous intervention involving the target lesion. There was a 42 percent reduction favoring stent implantation.

During the study, three patients died, one in the

Table 2. Angiographic Characteristics of the 516 Patients Included in the Intention-to-Treat Analysis and Characteristics of the Procedures They Underwent.*

Characteristic	Angioplasty (N = 257)	Stent (N = 259)
	number (percent)	
Artery dilated		
Right coronary	72 (28)	60 (23)
Left anterior descending	159 (62)	165 (64)
Left circumflex	26 (10)	34 (13)
Type of lesion†		
Concentric	118 (46)	130 (50)
Eccentric		
IA	33 (13)	34 (13)
IB	62 (24)	57 (22)
IIA	10 (4)	10 (4)
IIB	13 (5)	10 (4)
Tandem	0	1 (0.4)
Multiple irregularities	21 (8)	16 (6)
Occluded (TIMI 0 or 1)‡	5 (2)	9 (3)
Calcified	27 (11)	29 (11)
Length (mm)	6.96±2.57	7.06±2.56
Thrombus after procedure§	10 (4)	3 (1)
Dissection¶		
No	145 (56)	215 (83)
Type A	43 (17)	21 (8)
Type B	57 (22)	16 (6)
Type C	9 (4)	5 (2)
Type E	1 (0.4)	1 (0.4)
Type F	2 (0.8)	0
Nominal size, stent or balloon (mm)	3.29±0.38	3.31±0.34
Balloon/stent artery ratio	1.12±0.15	1.12±0.15
Largest balloon size (mm)‖	3.30±0.38	3.40±0.40
Maximal pressure (atmospheres)	9±3	10±8
Total inflation time (sec)	399±359	180±178

*The interobserver and intraobserver variability of these morphologic measures has previously been reported by the core laboratory.[13] Plus–minus values are means ±SD.

†According to the classification system of Ambrose et al.[14]

‡According to the TIMI Study Group.[10]

§According to the definition of Ellis et al.[15]

¶According to the classification system of Dorros et al.[16]

‖Nominal size.

Table 3. Frequency of Primary Clinical End Points in the Hospital and at Seven Months in Descending Order of Severity, Total Number of Events, and Quantitative Comparison of Immediate and Long-Term Angiographic Results.*

Event	Angioplasty (N = 257)	Stent (N = 259)	Relative Risk (95% CI)
	number (percent)		
Death			
In hospital	0	0	—
At 7 mo	1 (0.4)	2 (0.8)	1.98 (0.18–21.75)
All events	1 (0.4)	2 (0.8)	1.98 (0.18–21.75)
Cerebrovascular accident			
In hospital	1 (0.4)	0	—
At 7 mo	2 (0.8)	0	—
All events	2 (0.8)	0	—
Q-wave MI			
In hospital	2 (0.8)	5 (1.9)	2.48 (0.49–12.67)
At 7 mo	4 (1.6)	7 (2.7)	1.74 (0.51–5.86)
All events	5 (1.9)	7 (2.7)	1.39 (0.45–4.32)
Non–Q-wave MI			
In hospital	6 (2.3)	4 (1.5)	0.66 (0.19–2.32)
At 7 mo	6 (2.3)	4 (1.5)	0.66 (0.19–2.32)
All events	7 (2.7)	4 (1.5)	0.57 (0.17–1.91)
Urgent CABG			
In hospital	4 (1.6)	5 (1.9)	1.24 (0.34–4.57)
At 7 mo	4 (1.6)	5 (1.9)	1.24 (0.34–4.57)
All events	5 (1.9)	6 (2.3)	1.19 (0.37–3.85)
Elective CABG			
In hospital	0	3 (1.2)	—
At 7 mo	6 (2.3)	8 (3.1)	1.32 (0.47–3.76)
All events	6 (2.3)	10 (3.9)	1.65 (0.61–4.48)
Repeat PTCA			
In hospital	3 (1.2)	1 (0.4)	0.33 (0.03–3.16)
At 7 mo	53 (20.6)	26 (10.0)	0.49 (0.32–0.75)
All events	60 (23.3)	35 (13.5)	0.58 (0.40–0.85)
Any event			
In hospital	16 (6.2)	18 (6.9)	1.12 (0.58–2.14)
At 7 mo	76 (29.6)	52 (20.1)	0.68 (0.50–0.92)

Variable†	Angioplasty (N = 240)	Stent (N = 237)	P Value
	mean ±SD		
Reference diameter (mm)			
Before	3.01±0.46	2.99±0.45	NS
After	3.09±0.44	3.16±0.43	0.045
Follow-up	3.05±0.49	2.96±0.48	0.04
Minimal luminal diameter (mm)			
Before	1.08±0.31	1.07±0.33	NS
After	2.05±0.33	2.48±0.39	<0.001
Follow-up	1.73±0.55	1.82±0.64	0.09‡
Stenosis (%)			
Before	64±10	64±10	NS
After	33±8	22±8	<0.001
Follow-up	43±16	38±18	0.003
Restenosis rate (%)	32	22	0.02
Gain (mm)	0.97±0.39	1.40±0.44	<0.001
Loss (mm)	0.32±0.47	0.65±0.57	<0.001
Net gain (mm)	0.65±0.59	0.75±0.66	0.09

*"All events" refers to the total count of events at seven months (i.e., if a patient required repeat angioplasty and later coronary-artery bypass grafting, the total count at seven months would reflect both events, not just the first that occurred). CI denotes confidence interval, MI myocardial infarction, CABG coronary-artery bypass graft, PTCA percutaneous transluminal coronary angioplasty, and NS not significant.

†Reference values are the interpolated diameters of normal vessels; gain, the minimal luminal diameter after the procedure minus the value obtained before the procedure; loss, the minimal luminal diameter after the procedure minus the follow-up value; and net gain, the minimal luminal diameter at follow-up minus the value obtained before the procedure.

‡P = 0.08 and P = 0.03 for the difference in minimal luminal diameter between the two study groups at follow-up when the pre-intervention lumen and vessel size, respectively, were used as covariates.

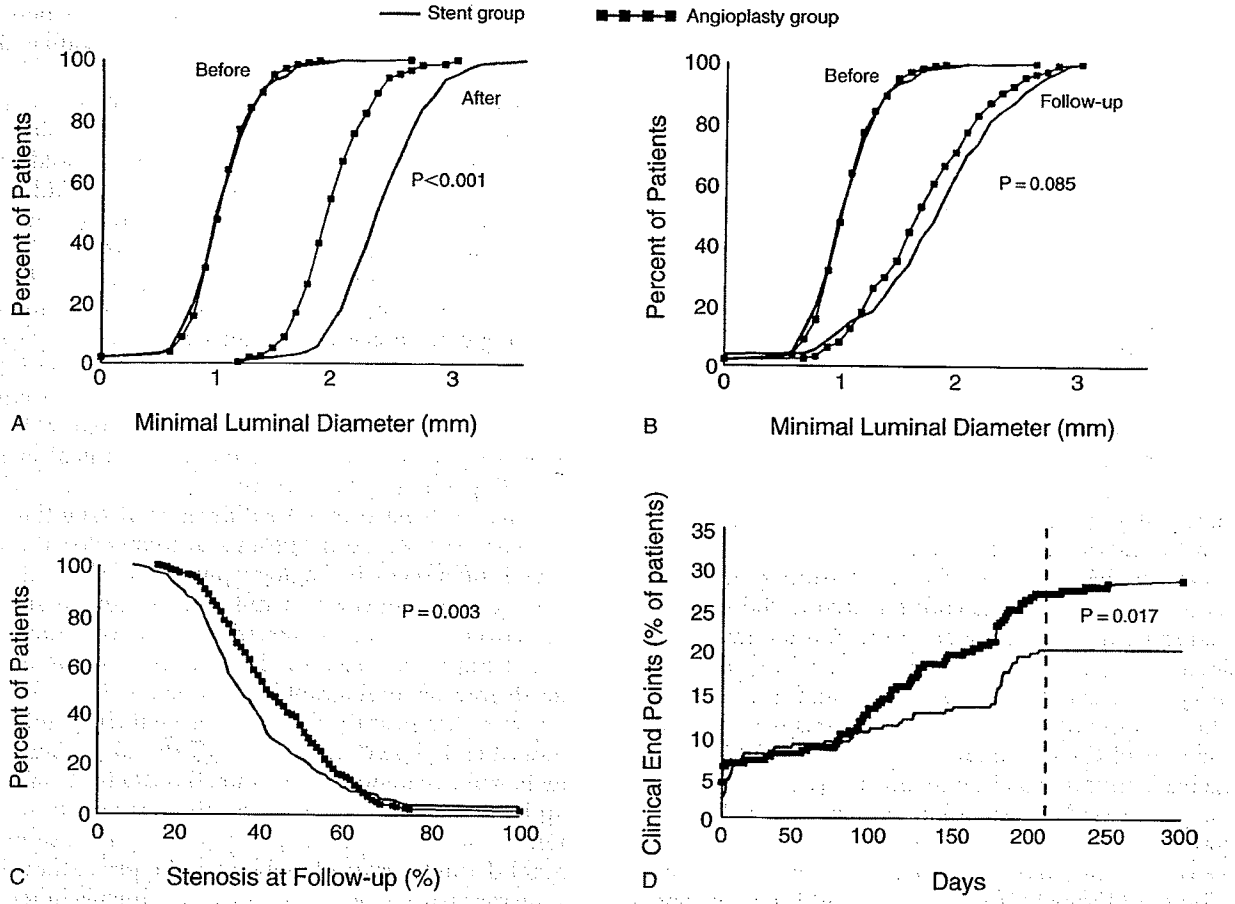

Figure 1. Cumulative Frequency Distribution Curves for the Two Study Groups, Showing Minimal Luminal Diameters Measured before and after Intervention and at Follow-up, the Percentage of Stenosis at Follow-up, and the Percentage of Patients with Clinical End Points.

Significant differences were apparent that consistently favored the stent group over the angioplasty group with respect to the increased minimal luminal diameter at intervention (Panel A) and follow-up (Panel B), the percentage of stenosis at follow-up (Panel C), and the incidence of major clinical events (Panel D). The vertical dashed line in Panel D indicates the end of the study.

angioplasty group and two in the stent group. One patient treated with balloon angioplasty committed suicide four months after the intervention. Two other patients died two and three weeks after successful stent implantations. In the first of these patients, death was preceded by chest pain associated with ST-segment elevation and was therefore thought to be related to a subacute occlusion. In the second patient, the cause of death was hypovolemic shock during surgical repair of an arteriovenous fistula. Although the stent was patent at the time of the pathological examination, the death was considered to be related to the stent.

Angiographic Analysis

Angiographic follow-up data were obtained for 93 percent of the eligible patients (Table 3). The minimal luminal diameter at follow-up was greater after stent implantation than after balloon angioplasty (1.82±0.64 vs. 1.73±0.55 mm, P = 0.09; median difference, 0.17 mm). The cumulative distribution of the minimal luminal diameter and percentage of stenosis are shown in Figure 1A, B, and C. The incidence of restenosis (the criterion for which was ≥50 percent stenosis) was 22 percent after stent implantation as compared with 32 percent after balloon angioplasty (P = 0.02).

Discussion

We found that implantation of coronary stents in patients with stable angina and a single new coronary-artery lesion was associated with a rate of immediate clinical success similar to that of standard balloon angioplasty, but a significantly lower rate of restenosis. This translated into a superior long-term clinical outcome, mainly due to a reduced need for additional percutaneous intervention, at least according to the composite analysis of clinical end points. The advantage of this combined clinical end point is that it leads to a simple estimate of the effect of treatment. However, this analysis ignores the relative effect of various events (i.e., it considers death, a cerebrovascular accident, myocardial infarction, and the like to be equally harmful to the patient) and does not reflect the multiplicity of events that may occur (e.g., in a patient undergoing second angioplasty and surgery and ulti-

Table 4. Functional Class at Seven Months of Follow-up or at the Time of the Intercurrent Intervention for the 516 Patients Included in the Intention-to-Treat Analysis.*

FUNCTIONAL CLASS†	ANGIOPLASTY (N = 257)	STENT (N = 259)
	number (percent)	
0 (Asymptomatic)	170 (66)	190 (73)
1–4	83 (32)	67 (26)
1	10 (4)	12 (5)
2	32 (12)	28 (11)
3	28 (11)	15 (6)
4	13 (5)	12 (5)
Unknown	4 (2)	2 (0.8)

*P = 0.07 for the comparison of functional classes according to treatment group (angioplasty vs. stent).

†The classes shown are those established by the Canadian Cardiovascular Society.

mately dying). To address this shortcoming, a count of all events is included in Table 3.

One of the major drawbacks of studies on the prevention of coronary restenosis is that at follow-up the angiographic knowledge of coronary anatomy may influence the physician's therapeutic decision and artificially increase the number of second interventions. This is especially true when the investigator is not kept unaware of the treatment assignments, as when a new device is tested. To circumvent this possible source of bias, a second intervention was considered an end point in this study only when it was substantiated on the basis of anginal symptoms or objective evidence of ischemia (Table 5). Only two second interventions in the angioplasty group and one in the stent group might not have been justified. Moreover, the fact that the cumulative curves for the composite clinical end points (Fig. 1D) diverged between day 75 and day 150 indicates that the difference in clinical outcome was not artificially driven by the angiographic findings at the time of the second catheterization.

Not unexpectedly, the incidence of major bleeding complications was significantly higher in the stent group (13.5 percent) than in the angioplasty group (3.1 percent). The overall incidence reported in the literature, expressed as a weighted average of groin hematomas and pseudoaneurysms, was 7.5 percent (range, 2.7 to 26 percent) and 4.2 percent (range, 0 to 10.8 percent), respectively.[17]

Table 5. Presence of Clinical Symptoms, Ischemic Signs, and Degree of Stenosis in Patients Who Underwent a Second Intervention at Follow-up.

VARIABLE*	ANGIOPLASTY (N = 257)	STENT (N = 259)
No. of patients	59	34†
No. with angina	54	31
No. with ECG changes at rest or during exercise	14	8
No. with neither angina nor ECG changes	2	1
No. with ETT performed	24	14
Percent stenosis — mean ±SD	59±14	66±21‡

*ECG denotes electrocardiographic, and ETT exercise-tolerance test.

†The relative risk as compared with the angioplasty group was 0.57 (95 percent confidence interval, 0.39 to 0.84; P = 0.005).

‡P = 0.06 for the comparison of groups by unpaired Student's t-test.

Another significant difference between the two treatment groups was in the duration of hospitalization. However, Cohen et al. recently showed that length of stay, consumption of resources, and total costs were still substantially greater for bypass surgery than for stenting and that the initially higher in-hospital costs of stent implantation as compared with balloon angioplasty are compensated for by the reduction in subsequent interventions during follow-up.[18,19] The practitioner and the patient must, however, weigh a long hospital stay and a 13.5 percent risk of bleeding and vascular complications against the potential benefit of a reduction in the likelihood of clinical events from 30 percent to 20 percent.

It may be argued that the difference in drug therapy between the two study groups accounts for the observed differences in angiographic outcome and rate of restenosis. However, a number of clinical studies collectively rule out any beneficial effect of anticoagulant therapy on restenosis in humans.[20-25] Moreover, the degree of angiographically documented luminal loss was significantly higher after stent implantation than after balloon angioplasty (Table 3). Therefore, the beneficial angiographic and clinical effects of stent implantation are explained by the propensity of the stent to achieve a consistently greater increase in luminal diameter immediately after the procedure than is the case with balloon angioplasty, which is inherently limited by the well-described phenomenon of elastic recoil.[3,26]

It should be emphasized that in interpreting the favorable results observed in this trial, the restrictive nature of the criteria for inclusion and exclusion must be kept in mind, and thus the results may not be generalizable to other patients, indications, and types of stents. Finally, bleeding and vascular complications and the prolonged hospitalization remain major drawbacks of stent implantation and continue to hamper its acceptance in clinical practice.

APPENDIX

The following institutions and investigators participated in the Benestent study. The number of patients enrolled at each center is given in parentheses.

University Hospital San Carlos, Madrid, Spain (76): F. Alfonso, J. Goicolea, R. Hernandez, and A. Iniguez; University Hospital Rotterdam Dijkzigt, Thorax Center, Rotterdam, the Netherlands (57): P.J. de Feyter and M. van den Brand; Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands (50): G.J. Laarman and R. vander Wieken; Universitätsklinikum Rudolf Virchow, Charlottenburg, Berlin, Germany (39): W. Rutsch; Onze Lieve Vrouwe Ziekenhuis, Aalst, Belgium (38): B. de Bruyne; Sahlgrenska Hospital, Goteborg, Sweden (36): P. Albertsson; Clinique Pasteur, Toulouse, France (32): J. Fajadet, S. Doucet, and O. Bar; Sart-Tilman Centre Hospitalier Universitaire, Liege, Belgium (32): V. Legrand; Hôpital de la Citadelle, Liege, Belgium (19): J. Boland; Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina (19): J. Berrocal and R. Piraino; Royal Brompton National Heart and Lung Institute, London (12): N. Buller and K. Priestley; Centro

Cuore Columbus, Milan, Italy (11): L. Maiello; Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (11): E. Eeckhout; Middelheim Ziekenhuis, Antwerp, Belgium (10): F. van den Brande; Gregorio Maranon, Madrid, Spain (10): E. Garcia; Ziekenhuis de Weezenlanden, Zwolle, the Netherlands (8): H. Suryapranata and J. Hoorntje; St. Antonius Ziekenhuis, Nieuwegein, the Netherlands (8): T. Plokker and G. Mast; Hospital Maggiore, Trieste, Italy (8): S. Klugmann, E. Della Grazia, and A. Salvi; Hôpital Cantonal Universitaire, Geneva, Switzerland (7): P. Urban and E. Camenzind; Academisch Ziekenhuis Groningen, Groningen, the Netherlands (6): P. den Heijer and R. van Dijk; Academic Medical Center, Amsterdam, the Netherlands (6): J. Piek and K. Koch; Christian Albrechts University, Kiel, Germany (6): R. Simon and G. Herrmann; Centre Cardiologique du Nord, Paris (5): M.C. Morice and T. Royer; St. James Hospital, Dublin, Ireland (5): P. Crean; Catharina Ziekenhuis, Eindhoven, the Netherlands (3): H. Bonnier, J. Koolen, and F. Bracke; Cliniques Universitaires St. Luc, Université Catholique de Louvain, Brussels, Belgium (2): W. Wijns; Centre Hospitalier Régional et Universitaire, Nancy, France (2): N. Danchin and Y. Juillière; and the Polyclinique Volney, Rennes, France (2): C. Bourdonnec.

Ethics and Safety Committee: F. Verheugt, Free University Amsterdam, Amsterdam, the Netherlands; J. Tijssen, Academic Medical Center, Amsterdam, the Netherlands; and G. de Backer, State University Ghent, Ghent, Belgium.

Steering Committee: P.W. Serruys (chairman), H. Emanuelsson, G.R. Heyndrickx, P.P.T. de Jaegere, F. Kiemeneij (co-chairman), C. Macaya, J. Marco, and P. Materne.

Critical Event Committee: F. Kiemeneij (chairman), P.W. Serruys, P.P.T. de Jaegere, P.J. de Feyter, and P. van den Heuvel.

Angiographic Assessment Committee: P.P.T. de Jaegere (chairman), P.W. Serruys, W. Rutsch, B. de Bruyne, and V. Legrand.

Exercise Testing Committee: V. Legrand (chairman), G. Laarman, and N. Danchin.

Data Coordinating and Analysis Center and Quantitative Angiographic Core Laboratory: Cardialysis, Rotterdam, the Netherlands: M. Morel, A.G. Azar, G.A. van Es, J.P. Herrman, R. Melkert, J. Pameyer, and L.M. Rodenburg.

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Sustained Suppression of Neointimal Proliferation by Sirolimus-Eluting Stents

One-Year Angiographic and Intravascular Ultrasound Follow-Up

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Background—We have previously reported a virtual absence of neointimal hyperplasia 4 months after implantation of sirolimus-eluting stents. The aim of the present investigation was to determine whether these results are sustained over a period of 1 year.

Methods and Results—Forty-five patients with de novo coronary disease were successfully treated with the implantation of a single sirolimus-eluting Bx VELOCITY stent in São Paulo, Brazil (n=30, 15 fast release [group I, GI] and 15 slow release [GII]) and Rotterdam, The Netherlands (15 slow release, GIII). Angiographic and volumetric intravascular ultrasound (IVUS) follow-up was obtained at 4 and 12 months (GI and GII) and 6 months (GIII). In-stent minimal lumen diameter and percent diameter stenosis remained essentially unchanged in all groups (at 12 months, GI and GII; at 6 months, GIII). Follow-up in-lesion minimal lumen diameter was 2.28 mm (GIII), 2.32 mm (GI), and 2.48 mm (GII). No patient approached the ≥50% diameter stenosis at 1 year by angiography or IVUS assessment, and no edge restenosis was observed. Neointimal hyperplasia, as detected by IVUS, was virtually absent at 6 months (2±5% obstruction volume, GIII) and at 12 months (GI=2±5% and GII=2±3%).

Conclusions—This study demonstrates a sustained suppression of neointimal proliferation by sirolimus-eluting Bx VELOCITY stents 1 year after implantation. (***Circulation.*** **2001;104:2007-2011.)**

Key Words: angiography ■ drugs ■ stents ■ restenosis ■ ultrasonics

Despite major technological advances in the past decades, of which the coronary stent is one of the most important, the percutaneous treatment of coronary artery disease is still hampered by a 20% to 30% incidence of restenosis. The list of candidate therapies and devices for prevention of restenosis after angioplasty is long and ever expanding. However, few if any have substantially improved the result of stenting for the treatment of de novo lesions. Intracoronary radiation has so far proven to be effective for the treatment of in-stent restenosis but not for the treatment of de novo lesions.[1] As a result of their ability to deliver prolonged and sufficient intramural drug concentrations to the target coronary segment, drug-eluting stents have emerged as a potential solution for restenosis. Our group has recently reported an almost complete absence of neointimal hyperplasia 4 months after implantation of sirolimus-eluting Bx VELOCITY stents.[2] The local release of sirolimus (rapamycin, Rapamune), a natural macrocyclic lactone with potent immunosuppressive action,[3] resulted in elimination of restenosis in this first series of patients. Comparable results have only been observed after the implantation of high-activity β-emitting stents (9 mm^3 of neointimal hyperplasia at 6-month follow-up).[4] However, a worrying late progression of in-stent neointimal hyperplasia was observed between 6 months and 1 year after implantation of radioactive stents.[5]

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The aim of the present investigation was to determine whether sirolimus-eluting stents produce a sustained suppression of the neointimal proliferation over a period of 1 year or merely delay the restenosis process.

Methods

Study Population

Forty-five patients with native coronary artery disease and angina pectoris were successfully treated with the implantation of a single

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From the Institute Dante Pazzanese of Cardiology (J.E.S., M.A.C., A.C.A., A.S.A., L.F.T., A.G.M.R.S.), São Paulo, Brazil; Thoraxcenter, Dijkzigt University Hospital (B.J.R., K.K., G.V.L. P.W.S.), Rotterdam, The Netherlands; Cordis, a Johnson and Johnson Company (R.F., J.J.), Warren, NJ; and Brigham and Women's Hospital (J.J.P.), Boston, Mass.

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sirolimus-eluting Bx VELOCITY stent. Only lesions ≤18 mm in length and vessels ≥3 and ≤3.5 mm in diameter were included. Total occlusion, ostial or thrombus containing lesions, unprotected left main disease with >50% stenosis, occurrence of myocardial infarction within the preceding 72 hours, and left ventricular ejection fraction <30% were the major exclusion criteria. Thirty patients were electively treated with two different formulations of sirolimus-eluting stents (fast release [FR], n=15, group I, and slow release [SR], n=15, group II) at the Institute Dante Pazzanese of Cardiology, São Paulo, Brazil. A third cohort of patients (n=15, group III) was treated with SR sirolimus-eluting stents at the Thoraxcenter, Erasmus University Rotterdam, The Netherlands.

Drug-Polymer Matrix and Elution Kinetics

Sirolimus was blended in a mixture of nonerodable polymers, and a 5-μm-thick layer of sirolimus-polymer matrix was applied onto the surface of the Bx VELOCITY stent (Cordis), a laser-cut 316L stainless-steel balloon-expandable stent.

The drug is almost completely eluted by 15 days after implantation in the FR formulation. Another layer of drug-free polymer was applied on top of the drug-polymer matrix to introduce a diffusion barrier and prolong drug release to >28 days in the SR formulation. All stents, regardless of the coating composition, were loaded with a fixed amount of sirolimus per unit of metal surface area (140 μg sirolimus/cm^2).

In vivo experiments have shown that sirolimus levels in whole blood peak at 1 hour (2.6±0.7 ng/mL, FR; 0.9±0.2 ng/mL, SR) after implantation and fall below the lower limit of quantification by 72 hours (0.4 ng/mL) (Bruce D. Klugherz, unpublished data, 2000). Taking into account that renal transplant patients maintain chronic blood levels of rapamycin between 8 and 17 ng/mL, the peak blood level after implantation of a sirolimus-eluting stent is absolutely negligible.

Stent Procedure

Stents were implanted according to standard practice, after balloon predilatation and followed by high-pressure (>12 atmospheres) balloon after dilatation. All stents were 18 mm long and 3 to 3.5 mm in diameter. Heparin was given to maintain the activated clotting time >300 seconds. Patients received aspirin (325 mg/d, indefinitely) started at least 12 hours before the procedure and a 300-mg loading dose of clopidogrel immediately after stent implantation and 75 mg/d for 60 days. The protocol was approved by the Medical Ethical Committees of both institutions, and written informed consent was obtained from every patient.

Angiographic and IVUS Procedures

Patients in São Paulo (groups I and II) underwent intravascular ultrasound (IVUS) and angiographic follow-up at 4 and 12 months. In Rotterdam (group III), patients returned for repeat angiography and IVUS assessment at 6 months, the classical restenosis time point. Intracoronary nitrates were administered immediately before each angiographic and IVUS acquisition. Postprocedure angiography was performed in at least 2 orthogonal projections, which were repeated at the follow-up studies. Quantitative angiographic analysis was done by an independent core laboratory (Brigham and Women's Hospital, Boston, Mass).

The segments subject to three-dimensional (3D) IVUS reconstruction were examined with a 30-MHz single-element mechanical transducer (ClearView, CVIS, Boston Scientific Corporation). A constant pullback speed of 0.5 mm/s was used for IVUS image acquisitions. A complete IVUS run was recorded on s-VHS tape for offline 3D reconstruction. At 12 months, IVUS images were also acquired using an ECG-triggered pullback device with a stepping motor at 0.2 mm/step (EchoScan, Tomtec) to assure a precise quantification of neointimal hyperplasia volume. This system acquires images coinciding with the peak of the R wave, eliminating the artifacts caused by the movement of the heart during the cardiac cycle and ultimately improving the quality of image for 3D volumetric quantification. Volumetric IVUS analysis was carried out by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands).[6,7]

Quantitative Measurements

Two coronary segments were subjected to quantitative angiography, in-stent and in-lesion segments. The in-stent analysis encompassed only the 18-mm-long segment covered by the stent. The in-lesion segment was defined as the stent plus 5 mm proximal and 5 mm distal to the edge or the nearest side branch. In-stent and in-lesion restenosis was defined as ≥50% diameter stenosis (DS) at follow-up, located within the stent and target lesion, respectively. Edge restenosis was defined as ≥50% DS at follow-up, located at the proximal or distal edge. Minimal lumen diameter (MLD) and percent DS were calculated for each segment.

Quantitative IVUS analyses of the stent segment were performed at all time points. Lumen and stent boundaries were detected using a minimum-cost algorithm. Total stent and lumen volumes were calculated as previously described. Intimal hyperplasia (IH) volume was calculated as stent volume minus luminal volume. Feasibility, reproducibility, and interobserver and intraobserver variability of these measurements have been validated previously.[8]

Statistical Analysis

Continuous variables are expressed as mean±SD. Comparisons between postintervention and follow-up measurements were performed with a 2-tailed paired t test. Comparisons between groups were performed using unpaired Student's t test. A P value <0.05 was considered statistically significant.

Results

Baseline characteristics were similar between the 3 groups. Overall, 29 patients were male, 32 had stable angina, and 13 were unstable. Mean age was 55.1 (group I), 57.9 (group II) and 60 years (group III). Six patients had a history of diabetes mellitus. Clopidogrel was discontinued at 60 days in all patients.

At the Thoraxcenter, 1 of the 15 patients died on day 2 of a cerebral hemorrhage. She had received abciximab during the procedure and for 12 hours thereafter. Two additional patients (group III) suffered a vessel occlusion during or immediately after the procedure attributable to distal edge dissection and were successfully treated with additional stenting. Subsequent clinical follow-up was uneventful for both patients, and no restenosis was detected at 6-month angiographic follow-up. Finally, 1 asymptomatic patient from Rotterdam refused repeat angiography; thus, 13 completed 6-month angiographic and IVUS follow-up. As reported previously,[2] all patients in groups I and II were discharged without any clinical event. One asymptomatic patient (group II) refused repeat angiography at 12 months.

A representative sequence of angiograms from a single patient are shown in Figure 1. Preprocedure reference vessel diameter (RD) was 2.85±0.46 mm, and postprocedure MLD was 2.47±0.38-mm (in-lesion) and 2.9±0.27-mm (in-stent) in the Rotterdam patients (group III). Four-month data from groups I and II have been reported previously.[2] One-year in-stent MLD (group I, 2.73±0.3 mm; group II, 2.87±0.4 mm) and percent DS (group I, 8.9±6.1%; group II, 6.7±7%) remained essentially unchanged compared with 4-month follow-up. At 6 months (group III), in-stent MLD was 2.66±0.3 mm, and percent DS was 8.9±7.6% (P=NS compared with postprocedure) Changes in in-lesion MLD and percent DS are shown in Figure 2. At 12 months,

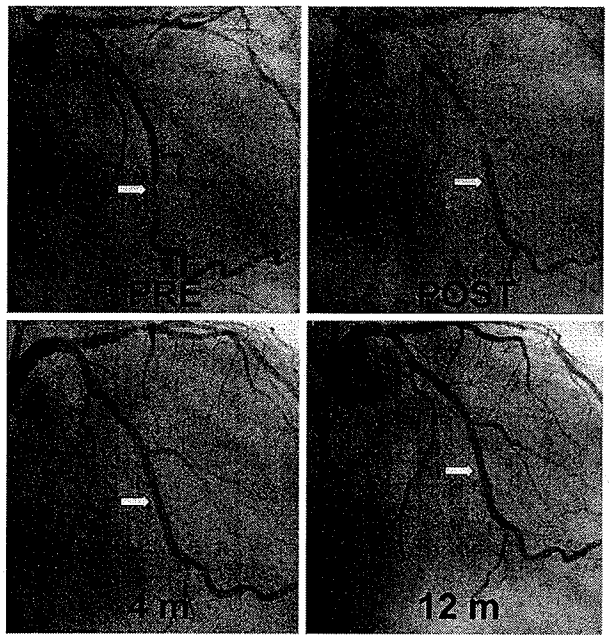

Figure 1. Angiography shows a lesion in the mid portion of the left circumflex marginal branch (white arrow), which was treated with the implantation of a sirolimus-coated BX-velocity stent (top right). Lumen dimensions remained unchanged at 4- and 12- month follow-up (bottom).

in-lesion angiographic lumen dimension showed a small decrease compared with postprocedure in both groups (Figure 2, $P<0.01$). Between 4 months and 12 months, a very small decrease, albeit statically significant ($P=0.004$), in in-lesion MLD was observed in group I. No patient approached the ≥50% DS at 1-year by angiography or IVUS assessment, and no edge restenosis was observed.

At 6-month follow-up, lumen volume was 156.7±63.6 mm^3 (versus 156.5±64.1 mm^3 at postprocedure, P=NS) and intimal hyperplasia volume was 5.7±17.7 mm^3 (group III). Thus, the percent obstruction volume was 2±4.98%, similar to the results reported at 4 months in the patients from São Paulo.[2]

One-year volumetric IVUS data (Figure 3) from the São Paulo patients were actually better than those reported previously at 4-month follow-up.[2] Only 2 patients had >10% IH after 12 months (Figure 3). Differences in the method of volumetric quantification probably explain these findings. As

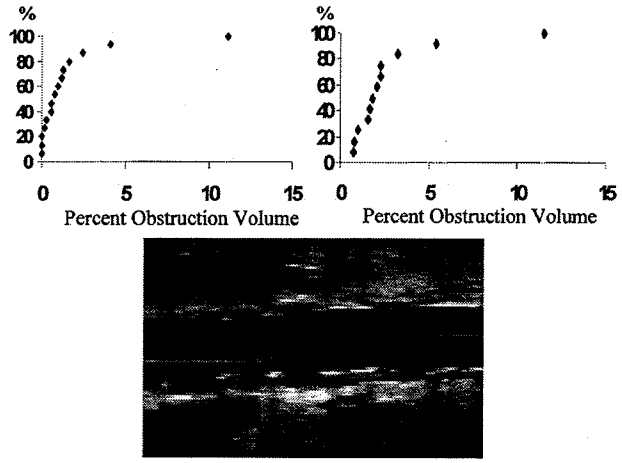

Figure 3. Cumulative distribution curves of percent obstruction volumes in group I (left) and group II (right) at 12-month follow-up. Longitudinal IVUS reconstruction illustrates the virtual absence of in-stent intimal hyperplasia at 12 months (bottom).

a result of the virtual absence of neointimal hyperplasia, the automated contour detection algorithm that was used for the original analysis superimposed the contours of the stent and lumen boundaries in the majority of the cases. Thus, the core laboratory analyst used a "copy and shrink" tool of the quantitative analysis software to dissociate the two contours. This action led to an overestimation of the amount of IH. At 12-month follow-up analysis, the lumen and stent contours were not dissociated artificially, unless IH was clearly visualized. To compare 4-month and 12-month IVUS data, the core laboratory reanalyzed the 4-month IVUS images using the same methodology used at 12 months (Table).

In one patient (group I), 12-month IVUS assessment showed an unstable plaque proximal to the stent. Lesion vulnerability was characterized by positive vessel remodeling and a large lipid pool delimited by a thin fibrous cap (Figure 4). This preexisting plaque increased progressively from the time of the initial procedure, producing a linear deterioration in lumen dimensions (MLD was 2.85 mm postprocedure, 2.51 mm at 4 months, and 2.02 mm at 12 months). No sign of thrombus was detected by angiography or IVUS. At 12 months, the patient was asymptomatic and had a negative stress test. However, at 14-month follow-up, he returned with a non–Q-wave myocardial infarction. Angiography showed

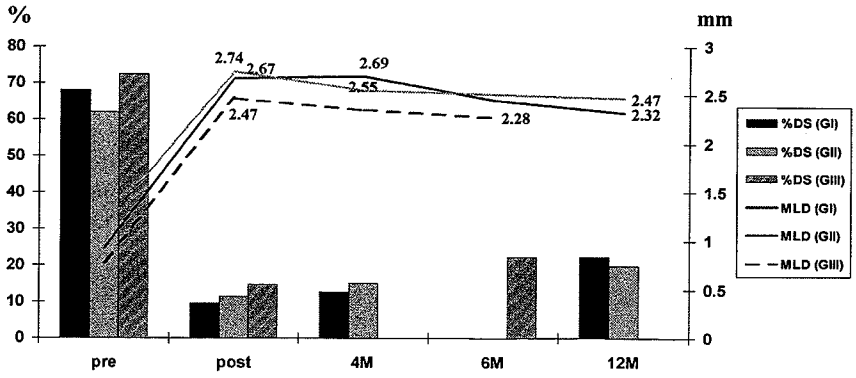

Figure 2. In-lesion percent diameter stenosis (%DS) and MLD over a period of 1 year. Angiographic follow-up was performed at 4 and 12 months in group I (GI) and GII and at 6 months in GIII.

Three-Dimensional Volumetric IVUS Measurements 4 and 12 Months After Implantation of Sirolimus-Eluting Stent

	Stent Volume, mm^3		Lumen Volume, mm^3		IH Volume, mm^3		Obstruction Volume, %	
Follow-up period, mo	4	12	4	12	4	12	4	12
Group I	134±30	127±26	134±30	124±25	0.4±0.8	3.2±8.5	0.3±0.6	2.3±5.5
Group II	138±21	127±30	137±22	124±30	0.3±0.9	2.5±3.4	0.3±0.8	2.2±3.4

No statistical differences were observed between groups or between 4-month and 12-month data within the same group.

the target vessel occluded proximal to the stent, and repeat angioplasty was performed.

The remaining 29 patients of the first 2 cohorts (groups I and II) have now completed 15-month clinical follow-up uneventfully. Similarly, the 14 Rotterdam patients were asymptomatic, with no additional adverse events up to 9 months after the index procedure.

Discussion

The present study demonstrates a potent, long-lasting inhibitory effect on neointimal proliferation exerted by the local release of sirolimus via a stent platform. Regardless of the coating formulation (SR or FR) or population treated (São Paulo or Rotterdam), neointimal hyperplasia, as detected by both angiography and volumetric IVUS quantification, was minimal at all time points (4, 6, or 12 months).

The lack of restenosis observed in this first series of patients treated with sirolimus-eluting Bx VELOCITY stents is probably a consequence of the scaffolding properties of the stent as well as the potent cytostatic effect of sirolimus.[9,10] Like cyclosporin A and tacrolimus (FK506), sirolimus binds to specific cytosolic proteins. However, the mechanism of action of sirolimus is distinct from other immunosuppressive agents that act solely by inhibiting DNA synthesis. The sirolimus:FKBP complex binds to a specific cell-cycle regulatory protein, the mTOR (mammalian target of rapamycin), and inhibits its activation.[11] The inhibition of mTOR induces cell-cycle arrest in late G1 phase.[12–14] The upregulation of FK506-binding protein 12 (FKBP12) observed in human neointimal smooth muscle cells additionally supports the potential antirestenotic effect of sirolimus.[15] Preclinical data have demonstrated the efficacy of both systemic[13,16] and local administration (via drug-eluting stent) (Andrew J. Carter, unpublished data, 2000) of sirolimus in reducing neointimal hyperplasia in different models of restenosis.

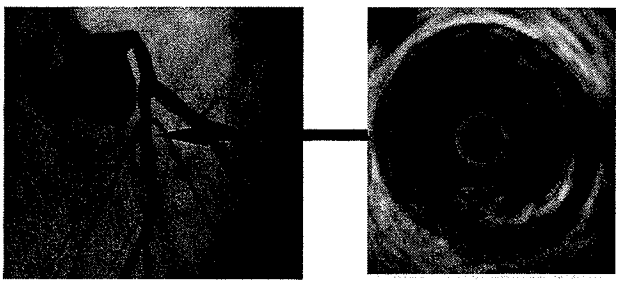

Figure 4. Angiography of the left anterior descending artery showing a nonsignificant stenosis at the proximal edge of the stent (white arrow) at 12-month follow-up. IVUS cross-sectional image at the site of the lesion shows an eccentric plaque with a large lipid pool (L) delimitated by a fibrous cap (arrows). This vessel was occluded 2 months later.

A concern about potential late complications, such as late thrombosis, associated with new therapies is a legacy from our previous experience with intracoronary radiation therapy.[17] In our series, one patient (out of 44) experienced a thrombotic event involving the target coronary artery 14 months after the procedure. It is important to note that IVUS showed an unstable plaque located proximal to the stent that grew progressively in size over the period of observation. The relationship between unstable plaque, as characterized by IVUS, and coronary thrombosis has been reported previously and may explain this unexpected event.[18,19] Experimental investigations have shown a similar degree of re-endothelialization between bare and sirolimus-coated stents occurring as early as 30 days after implantation (Andrew J Carter, unpublished data, 2001), ie, sirolimus does not seem to delay endothelialization. Nevertheless, one cannot completely rule out the possibility of late-stent thrombosis as a cause of vessel occlusion in this case. The occurrence of this somewhat anecdotal event should be interpreted with caution. Data from large randomized multicenter trials, already underway, will be necessary to definitively address this important question.

After our previous study showing a surprising near-absence of IH 4 months after implantation of sirolimus-eluting stents,[2] the logical question was whether this effect would be permanent or whether it merely represented a delay in the proliferative response. The basis for these concerns is the unexpected late-luminal deterioration observed with catheter-based radiation systems and radioactive stents,[1,5] although the mechanisms of action of sirolimus-eluting stents differ considerably from intracoronary brachytherapy. In the present study, angiographic lumen dimensions and IVUS-detected IH volume assessed both at 6-month follow-up (in group III) and at 12 months (groups I and II) was not substantially different from what was observed at 4 months (Table). Thus, at 12-month follow-up, there is no evidence of significant late catch up, and the 12-month IH volume observed in the present study is less than one third of that reported with any previously tested antirestenosis therapy.[6,7] If the findings of the present investigation are confirmed by large, randomized, placebo-controlled trials, this technology is likely to have a major impact on the treatment of coronary artery disease in the near future.

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CERTIFICATE OF SERVICE

I hereby certify that on the 9th day of October, 2009, the attached **APPENDIX OF EXHIBITS TO DEFENDANTS/COUNTER-PLAINTIFFS JOHNSON & JOHNSON AND CORDIS'S RESPONSE TO PLAINTIFFS' OPENING MARKMAN BRIEF** was served upon counsel of record at the address and in the manner indicated:

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/s/ Lauren E. Maguire

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I hereby certify that on the 19th day of October, 2009, the attached **REDACTED PUBLIC VERSION OF APPENDIX OF EXHIBITS TO DEFENDANTS/COUNTER-PLAINTIFFS JOHNSON & JOHNSON AND CORDIS'S RESPONSE TO PLAINTIFFS' OPENING MARKMAN BRIEF** was served upon counsel of record at the address and in the manner indicated:

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